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AEROBIC OXIDATION OF ALCOHOLS WITH HOMOGENEOUS CATALYSTS BASED ON NITROXYL RADICALS

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ACADEMIC DISSERTATION

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Abstract

The selective oxidation of alcohols to aldehydes, ketones and carboxylic acids is among the pivotal reactions in organic chemistry. Traditionally, the transformation is conducted using stoichiometric amounts of heavy metal oxidants, which are costly and their use produces large amounts of hazardous waste. In this respect, the development of catalytic methods, which use oxygen as the oxidant and produce water as sole by-product, is crucial from the sustainable point of view. Recently, aerobic oxidation catalysts based on the combined used nitroxyl radicals and different co-catalysts have gained considerable amount of research interest due to their excellent performance in selective oxidation of alcohols under very mild conditions.

The literature section of this thesis covers the selective aerobic oxidation of alcohols to carbonyl and carboxylic compounds with homogeneous catalysts based on the use of nitroxyl radicals together with different oxygen-activating co-catalysts. The experimental section presents the central findings and discussions from the author's peer reviewed publications. In the first part, a catalytic oxidation method based on the combined use of nitroxyl radicals with Fe-based co-catalyst system is described. The method enables the oxidation of primary alcohols selectively either to aldehydes or carboxylic acids under mild conditions. The second part focuses on a catalyst system that is based on combined use of nitroxyl radicals and a Mn-based co-catalyst system. This catalytic method provides a highly practical way to selectively oxidize primary and secondary alcohols to aldehydes and ketones using simple reaction setup and workup procedures. The third section presents a further improved version of the aforementioned nitroxyl radical/Mn catalyst, which allows the oxidation of alcohols to be performed with very high efficiency using a small amount of catalyst.

Preface

This work was conducted at the Department of Chemistry, University of Helsinki between January 2014 and March 2018.

I want to express my deepest gratitude to Professor Timo Repo for providing me with the opportunity to work under his supervision. I thank him for encouraging me to pursue the ambitious ideas and for the support he gave me during the challenging times of my work. I feel very fortunate having been able to conduct this work without needing to stress about funding too much, as the work was constantly financed by funding from the Academy of Finland.

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I want to acknowledge my dearest friend Teemu Myllymäki for his support and friendship. Working in our common company Measur and spending time with him has taught me persistence and given me the motivation to push hard with my academic work. I am deeply thankful to my parents Esko and Riitta for their constant love, encouragement and financial support during the long years of my studies. Without their support, this thesis would not exist. Finally, I want to thank Emmi for her love, patience and understanding. Her respectful words have helped me in my work more than she could believe.

List of original publications

This thesis is based on the following publications:

I Lagerblom, K., Wrigstedt, P., Keskiväli, J., Parviainen, A. and Repo, T.: Iron-Catalysed Selective Aerobic Oxidation of Alcohols to Carbonyl and Carboxylic Compounds. *ChemPlusChem*, **2016**, 81, 1160-1165.

II Lagerblom, K., Lagerspets, E., Keskiväli, J., Cook, C., Ekholm, F., Parviainen, A., & Repo, T.: Practical Aerobic Oxidation of Alcohols: A Ligand Enhanced 2,2,6,6 - Tetramethylpiperidine - 1 - oxy/Manganese Nitrate Catalyst System. *ChemCatChem*, **2017**, 9, 3880-3887.

III Lagerblom, K., Keskiväli, J, Parviainen, A., Mannisto J.: Selective Aerobic Oxidation of Alcohols with NO_3^- Activated Nitroxyl Radical/Manganese Catalyst System. *ChemCatChem*, **2018**, in press. DOI: 10.1002/cctc.201800438

The publications are referred to in the text by their roman numerals.

Author's contribution

Publication I: The author performed the majority of the planning, experimental work and analyses. Some experimental work was performed by Dr. Arno Parviainen, Dr. Pauli Wrigstedt and Dr. Juha Keskiväli. The work was conducted under the supervision of Prof. Timo Repo. The author drafted the manuscript and all authors took part in preliminary revision of the paper.

Publication II: The author performed the majority of the planning, experimental work and analyses. UV-vis measurements were performed by Emi Lagerspets. Minor experiments were performed by Dr. Filip Ekholm, Dr. Juha Keskiväli and Chris Cook. The work was conducted under the supervision of Prof. Timo Repo. The author drafted the manuscript with the help of Dr. Arno Parviainen and all authors took part in preliminary revision of the paper.

Publication III: The author performed the majority of the planning, experimental work and analyses. Minor experiments were performed by Jere Mannisto and Dr. Juha Keskiväli. The work was conducted under the supervision of Prof. Timo Repo. The author drafted the manuscript and all authors took part in preliminary revision of the paper.

Abbreviations

1-Me-AZADO	1-methyl-2-azaadamantane-*N*-oxyl
5-F-ABNO	5-fluoro-2-azaadamantane-*N*-oxyl
ABNO	9-zzabicyclo[3.3.1]nonane *N*-oxyl
AcOH	acetic acid
AZADO	2-azaadamantane-*N*-oxyl
bipy	2,2'-bipyridine
[bmim][PF_6]	1-butyl-3-methylimidazolium hexafluorophosphate
Boc	*tert*-butyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFF	2,5-diformylfuran
DMAP	dimethylaminopyridine
DMF	dimethylformamide
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
GO	galactose oxidase
h	hour
HMF	5-(hydroxymethyl)furfural
IR	infrared
keto-ABNO	9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl
KIE	kinetic isotope effect
MeCN	acetonitrile
MeObipy	4,4'-dimethoxy-2,2'-bipyridine
min	minute
MOF	metal-organic framework
Nitroxide	nitroxyl radical
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
nor-AZADO	9-azanoradamantane *N*-oxyl

p-TSOH	*para*-toluenesulfonic acid
PMB	*para*-methoxybenzyl
PyCOOH	2-picolinic acid
[Quaternium-TEMPO]	*N,N*-dimethyl-(4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl)dodecyl
RT	room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxyl
TEMPOH	1-hydroxy-2,2,6,6-tetramethylpiperidine
$TEMPO^+$	2,2,6,6-tetramethylpiperidine- 1-oxonium
UV–vis	ultraviolet–visible spectroscopy

1 Introduction

The annual production of carbonyl compounds has been estimated to be over 10^7 tons and a significant proportion of these compounds are produced through the oxidation of alcohols.[1,2] In this light, the selective conversion of alcohols to carbonyl compounds is among the pivotal reactions in organic chemistry.[3] Traditionally, the transformation is conducted using stoichiometric oxidants, such as Cr[4] and Mn[5] oxides, hypervalent iodine[6] or activated DMSO[7], which are costly, toxic and their use produces large amounts of hazardous waste.

From the sustainability point of view, O_2 is an ideal oxidant because of its abundancy and tendency to form H_2O as a sole by-product in oxidation reactions.[8] However, there are two major issues concerning the use of O_2 for alcohol oxidation: O_2 is a four-electron oxidant, while the oxidation of alcohol to a carbonyl compound involves loss of two electrons. Moreover, the O_2 molecule exists in a triplet ground state and its reaction with a singlet state alcohol molecule is spin-forbidden and therefore very slow. For these reasons, a suitable electron transfer catalyst must be employed in the aerobic oxidation of alcohols to facilitate the reaction between triplet oxygen and the singlet state substrate in a controlled manner.

During the past decades, a number of catalytic methods have been reported for the aerobic oxidation of alcohols, many based on noble metals, such as Pd, Ru, and Au.[9–12] Despite the promising results obtained with these catalysts, their applicability to practical synthesis is constrained by high catalyst prices, restricted substrate scopes, frequent use of halogenated solvents and safety concerns related to the use of flammable reagents under high pressures of O_2.[13–16] Accordingly, there is a high demand for affordable and efficient catalysts that enable oxidation of various alcohols under under mild reaction conditions.

In the search for new catalytic methods, intriguing results have been achieved with homogeneous catalysts that are based on the combined use of nitroxyl radicals (nitroxides), such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and oxygen activating co-catalysts, such as Fe salts and oxides of nitrogen (NO_x).[17,18] These catalysts have been shown to mediate the selective aerobic oxidation of alcohols under very mild reaction conditions without the need for toxic or hihgly expensive catalyst components, high pressures of pure O_2 or halogenated solvents.

2 Scope of the thesis

This thesis covers the selective aerobic oxidation of alcohols to carbonyl and carboxylic compounds with homogeneous nitroxyl radical (nitroxide) catalysts. The literature review begins with brief introductions to dioxygen and nitroxides, which are given in chapters 3.1 and 3.2. This is followed by reviews of different co-catalyst systems that are used in combination with nitroxides to mediate the aerobic oxidation of alcohols. First, the most widely studied Cu and Fe-based co-catalysts are discussed in chapters 3.3 and 3.4. Then, the less explored catalysts based on the combined use of other transition metals and nitroxides are reviewed in chapter 3.5. Finally, transition-metal-free nitroxide catalysis is discussed in chapter 3.6.

The literature review presents the background to the experimental part of the work, which aimed to develop new nitroxide-based catalytic methods for the aerobic oxidation of alcohols and to build understanding on the catalysts' structure-reactivity relationships. To achieve these objectives, a great deal of work was conducted to screen potential catalyst materials and study the reaction mechanisms as well as to optimize the reaction conditions and work-up procedures. This work is described in chapter 4, which highlights and discusses the central findings in the author's publications **I-III**. In article **I**, a novel Fe/nitroxide-based catalyst system is described, which enables one-step oxidation of primary alcohols selectively either to aldehydes or carboxylic acids and secondary alcohols to ketones. Publication **II** covers the selective oxidation of primary and secondary alcohols with a novel and highly practical Mn/nitroxide catalyst system. In publication **III**, a further improved and version of the above Mn/nitroxyl radical catalyst is presented, which allows efficient and highly selective oxidation of alcohols using low catalyst loading.

3 Review of the literature

3.1 Oxygen and aerobic oxidation

Oxygen is a highly abundant element on Earth, consisting of 21% of the atmosphere by volume and almost half of Earth's crust by mass.[19] It has an electronic structure of $1s^2\ 2s^2\ 2p^4$, which gives rise to its molecular structure of O_2 with two unpaired electrons in a triplet ground state. Oxygen is the second most electronegative element after fluorine, making it a strong oxidizer that reacts with most organic molecules under suitable conditions. However, direct reactions between the triplet state of O_2 and singlet state organic molecules are spin forbidden and therefore very slow. The reactivity of O_2 towards organic molecules can be increased by chemically or photonically exciting O_2 to a singlet state.[20] However, the existing excitation processes suffer from poor efficiencies and are therefore seldom applied in synthetic chemistry. More often, O_2 is activated for synthetic purposes by using catalysts, which mediate the reactions between triplet state oxidant and singlet state substrate.[21] Research on such catalysts has been active for over a hundred years and numerous synthetically useful methods utilizing O_2 as an oxidant for organic molecules have been developed.[22]

The first report on using O_2 for the selective oxidation of alcohols dates back to 1984, when Semmelhack and co-workers[23] published their landmark paper describing the selective aerobic oxidation of primary alcohols to aldehydes. Since then, various aerobic alcohol oxidation protocols have been published. However, many of the developed catalyst systems are based on the use of noble metals (e.g., Pd, Au & Ru), expensive activating ligands, or require the use of high pressures of pure O_2 together with flammable reagents, which limits their use due to economic and safety reasons.[9,15,24,25] Accordingly, inexpensive alcohol oxidation catalysts that utilize ambient air as the oxidant are highly sought after and the topic has gained significant amount of research scrutiny lately. Very promising results have been obtained by using catalyst systems that are based on the combined use of nitroxyl radicals and oxygen-activating co-catalysts. These catalyst systems will be discussed in detail in the following chapters.

3.2 Nitroxyl radicals (nitroxides)

Nitroxyl radicals (nitroxides) are molecules possessing an *N,N*-disubstituted N-O$^{\bullet}$ group with an unpaired electron. The first nitroxide, porphyrexide (Figure 3.2.1) was discovered in 1901 by Piloty and Schwerin.[26,27] The discovery of porphyrexide was followed by synthesis of diaryl nitroxides such as diphenyl nitroxide by Wieland and Offenbächer in 1914.[28] These nitroxides

have widely conjugated electronic structures in which the unpaired electron is delocalized over the entire molecule. Conjugated nitroxides are generally unstable because migration of the unpaired electron leads to C-C bond formation and fission within the carbon backbone of the molecule.[29] Therefore, the use of nitroxides as reagents or catalysts in organic synthesis did not become common practice before the first non-conjugated nitroxide 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was synthesized and characterized by Lebedev and Kazarnovskii in 1959.[30] In TEMPO, the unpaired electron is delocalized only over the N-O bond, which diminishes decomposition of the molecule through C-C bond formation and fission.[29] Therefore, TEMPO is stable enough to be used as a catalyst in organic reactions.[31]

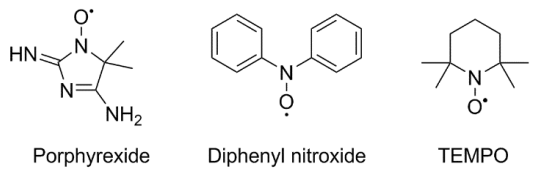
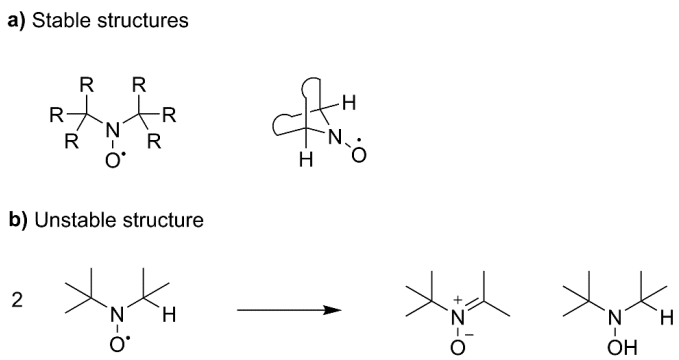


Figure 3.2.1. Structures of selected nitroxides.

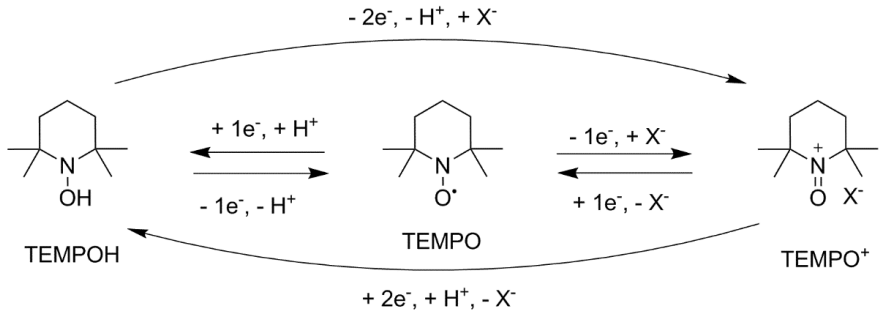
Non-conjugated nitroxides are generally stable if the structures lack α-hydrogens or have bicyclic structures that prohibit the formation of double bonds between the nitrogen and the adjacent carbon atom (Scheme 3.2.1a).[29,32] If hydrogen atom(s) are present in the α-position and double bond formation is allowed according to Bredt's rule, nitroxides disproportionate to form a nitrone and a hydroxylamine (Scheme 3.2.1b).[33,34]



Scheme 3.2.1. Structure examples of a) stable nitroxides b) unstable nitroxide.

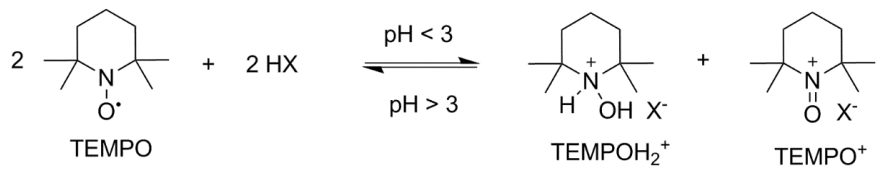
Due to their unique redox properties and high stabilities, non-conjugated nitroxides are often used as oxidants and oxidation catalysts for organic

reactions.[17,35–37] In particular, TEMPO is a widely used catalyst for alcohol oxidation. One electron reduction of TEMPO produces the hydroxylamine TEMPOH and one electron oxidation yields the respective oxoammonium cation $TEMPO^+$.[38] Two electron reduction of $TEMPO^+$ produces TEMPOH, which may be converted back to TEMPO or $TEMPO^+$ through one or two electron oxidation, respectively.



Scheme 3.2.2. Redox chemistry of TEMPO.

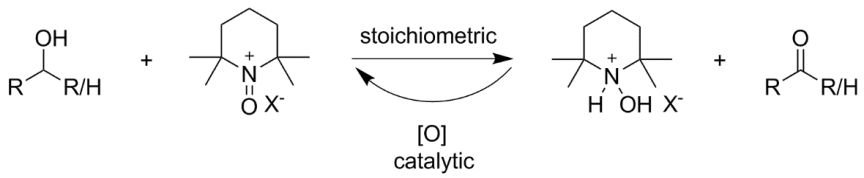
Under acidic conditions (pH < 3) two molecules of TEMPO undergo disproportionation to protonated $TEMPOH_2^+$ and $TEMPO^+$ (Scheme 3.2.3).[39,40] The reaction is reversed at pH > 3, leading to comproportionation of $TEMPOH_2^+$ and $TEMPO^+$ to produce two TEMPO molecules.



Scheme 3.2.3. Reversible disproportionation of TEMPO.

Oxoammonium cations, such as $TEMPO^+$ react stoichiometrically with alcohols, affording hydroxyl amines and carbonyl compounds (Scheme 3.2.4).[37,41] The reaction is generally highly selective; primary alcohols can be oxidized to aldehydes with very little over-oxidation to carboxylic acids or C-C bond cleavages taking place.[37] This alcohol oxidation can be made catalytic with respect to oxoammonium cation, if an additional oxidant is used for converting the formed hydroxyl amine back to an oxoammonium cation. Numerous oxidants, including cerium(IV) ammonium nitrate,[42] 3-chloroperbenzoic acid,[43] NaOCl,[44] Oxone®,[45] $PhI(OAc)_2$,[46] and trichloroisocyanuric acid,[47] have been used for this purpose. Selective

oxidation of alcohols can be achieved using these terminal oxidants, but the use of such oxidants results in poor atom economy and high e-factor. In this respect, using O_2 as a terminal oxidant would be ideal, as it bears no unreactive atoms and H_2O is generally the sole byproduct. However, due to spin conservation rule, O_2 does not readily react with hydroxyl amines to produce oxoammonium cations. Yet, the aerobic oxidation of alcohols can be achieved with nitroxide catalysts in the presence of suitable oxygen activating co-catalysts, such as transition metals or nitrogen oxides (NO_x) which will be discussed in the following chapters.



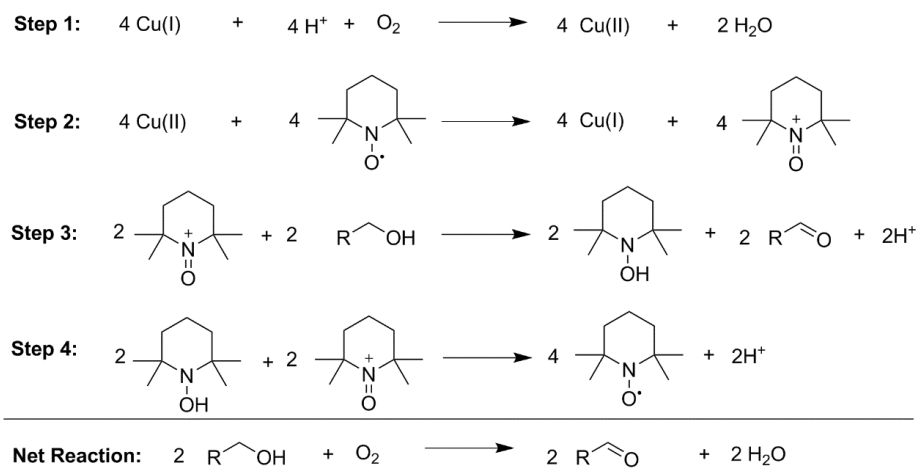
Scheme 3.2.4. Reaction of alcohol with oxoammonium ion produces carbonyl compound and hydroxylamine.

3.3 Copper co-catalysts

For a long time, nature has been an important source of inspiration for synthetic chemists, who have tried to observe and recreate enzyme catalyzed reactions in the laboratory.[48] Aerobic oxidation chemistry has been driven forward by mimicking the action of naturally occurring metalloenzymes that mediate numerous oxidative reactions in living cells.[49] Among the most studied oxidation enzymes is galactose oxidase (GO), a mononuclear Cu-enzyme, which mediates the aerobic oxidation of primary alcohols to aldehydes in some species of fungi.[50] The active site of GO consists of a Cu(II)-center surrounded by protein-bound amino acid ligands.[51] The activity of GO stems from the tendency of one of these ligands to undergo one electron oxidation to form a radical species which, together with Cu(II) center, accepts two electrons from an alcohol molecule, converting it to an aldehyde.[52]

The coupling of a radical ligand with Cu in GO has inspired researchers to try a similar strategy when developing synthetic aerobic oxidation catalysts for alcohols. The first study adapting this approach was published by Brackman and Gaasbeek[53] in 1966, when they reported that the presence of a di-tert-butylnitroxyl radical facilitates the Cu(II)/phenanthroline-catalyzed aerobic oxidation of methanol to formaldehyde and formic acid. However, the topic of aerobic oxidation of alcohols did not catch the attention of the broad scientific community until 1984, when Semmelhack and co-workers[23] published their landmark study. In that work, Semmelhack reported that various alcohols can

be selectively oxidized to carbonyl compounds under O_2 bubbling in DMF solution at room temperature with a catalyst consisting of CuCl (10 mol%) and TEMPO (10 mol%). The method is efficient for selective oxidation of benzylic and allylic primary alcohols to the respective aldehydes, but only poor yields of carbonyl compounds can be obtained with aliphatic primary alcohols and secondary alcohols as substrates. The authors proposed a reaction pathway, which begins by oxidizing Cu(I) to Cu(II) with O_2 (Scheme 3.3.1, **step 1**). Then, Cu(II) reacts with TEMPO, forming Cu(I) and the oxoammonium cation $TEMPO^+$ (**step 2**). The latter oxidizes alcohol to aldehyde being itself reduced to the hydroxylamine TEMPOH (**step 3**). Regeneration of the initial nitroxide TEMPO takes place through comproportionation of TEMPOH and $TEMPO^+$ (**step 4**).



Scheme 3.3.1. The proposed mechanism for the CuCl/TEMPO-catalyzed aerobic oxidation of alcohols by Semmelhack and co-workers.[23]

In Semmelhack's publication, aliphatic alcohols were sluggishly oxidized to aldehydes, although other reports suggest that the transformation would readily occur if oxoammonium cations were present in the solution, as the authors had proposed.[36,41] This inconsistency motivated Sheldon and co-workers[54–56] to investigate the reaction in more detail. The findings in Sheldon's studies provided strong evidence that Cu/nitroxide catalyzed aerobic alcohol oxidation does not proceed through the reaction of an oxoammonium ion with alcohol, as Semmelhack had suggested, but a Cu-nitroxide complex is the likely active oxidant instead. Sheldon's theory has since been supported by numerous publications by other auhtors including Falk,[57] Koskinen,[58] Stahl,[59–61] and Iwabuchi.[62]

The studies published after Semmelhack's initial work have shown that catalytic activity of Cu/nitroxide oxidation catalysts can be greatly increased if a catalytic amount of coordinating ligand and base are added into the

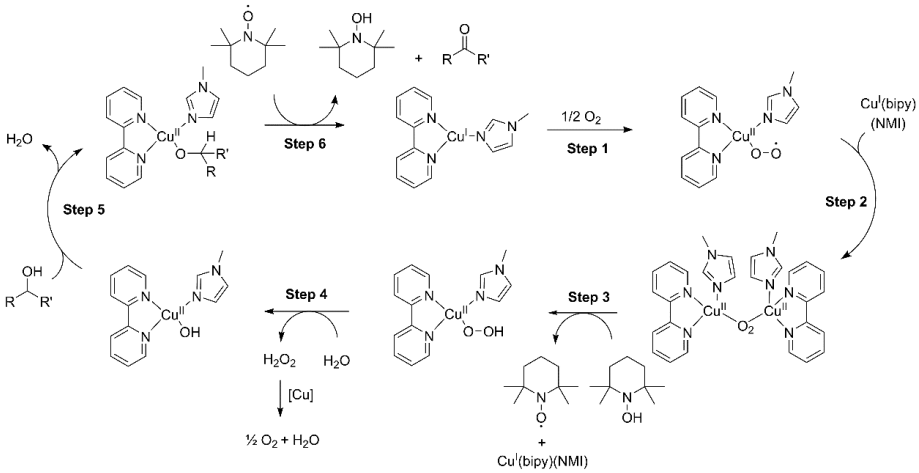
reaction.[55,56] Among the various ligands explored, bidentate N,N-donor ligands, such as 2,2-bipyridine (bipy), phenanthroline and the electron donating derivatives of the former (e.g. 4,4-dimethoxy-bipy or 4,4-di-*tert*-butyl-bipy) have been proven efficient for activating Cu-based catalysts.[56,58–61] Also other ligands, including salen,[63] pyrazole-pyridine,[64] 2-*N*-arylpyrrolecarbaldimine,[65] chiral binaphthyls[66,67] and nonfluoroponytailed nitrogen compounds,[68] have been utilized, but these ligands have often failed to outperform the relatively cheap and easily available bipy and its analogues. Studies focusing on the effect of different bases on the catalyst activity have shown that good catalytic performance is achieved using N-donor bases with weak Lewis-basicity, such as N-methylimidazole (NMI) and 4-dimethylaminopyridine (DMAP).[58,59,61,62] Stronger bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO), give rise to higher initial alcohol oxidation rates, but lead to fast catalyst deactivation through formation of insoluble Cu hydroxides and oxides.[58]

Throughout the years, various Cu(I) and Cu(II) salts have been used as precursors for catalyst preparation. Among the used metal salts, highest catalytic activities have generally been achieved with Cu(I) salts, such as CuBr and $Cu(MeCN)_4OTf$.[59–62]

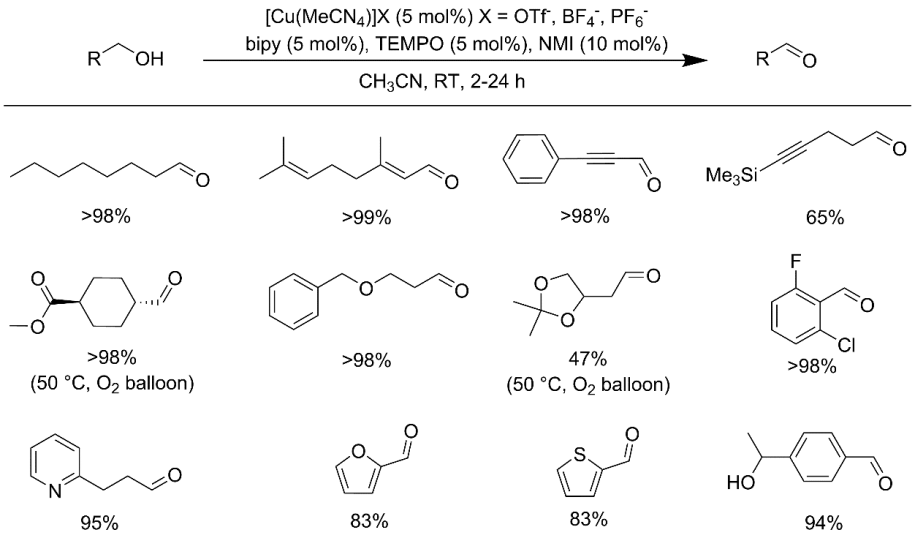
The majority of the Cu/nitroxide-catalyzed aerobic alcohol methods utilize acetonitrile (MeCN) or aqueous mixtures of MeCN as solvent, but the use of other solvents, such as H_2O[65,69] DMSO[70] and biphasic chlorobenzene/perfluoro octane[71] have been explored as well. In addition to conventional solvents, the use of ionic liquids as oxidation media has also attracted attention, but efficiencies comparable to those obtained in MeCN have not been achieved to date.[72–75]

Numerous mechanistic proposals have been presented for the Cu/nitroxide-catalyzed aerobic oxidation of alcohols.[54,55,58,60–62] Plausibly the most extensive works, involving electron paramagnetic resonance-spectroscopy, gas chromatography, O_2 uptake measurements, *in situ* infrared spectroscopy, cyclic voltammetry, UV-visible spectroscopy (UV-vis) and density functional theory calculations have been published by Stahl and co-workers.[60,61] In these publications, the authors suggested a multistep reaction mechanism, which begins with the reaction of a Cu(I) complex with O_2 to form a Cu(II)-superoxide species. This then reacts with a second Cu(I) complex, forming a peroxo-bridged binuclear Cu(II) species (Scheme 3.3.2, **steps 1** and **2**). The formed binuclear Cu(II) species then oxidizes TEMPOH to TEMPO, being itself converted to Cu(II)-OOH and Cu(I) as a byproduct (**step 3**). Subsequent reaction of the Cu(II)-OOH species with water affords a Cu(II)-OH intermediate and releases hydrogen peroxide, which rapidly decomposes in the presence of Cu (**step 4**). The alcohol substrate then coordinates to Cu(II), forming a Cu(II)-alkoxide intermediate and releasing water (**step 5**). Finally, the alcohol is oxidized Cu(II) and TEMPO, releasing the carbonyl product and the initial Cu(I) complex (**step 6**).

Stahl and co-workers[59] have also showed that the Cu(I)/bipy/TEMPO/NMI catalyst system has a broad substrate scope by performing oxidation of various substrates, including alcohols with alkyne, amine, ether and thioether functionalities (Scheme 3.3.3). On the other hand, the authors discovered that the Cu(I)/bipy/TEMPO/NMI catalyst system also has some substrate scope limitations. For example, oxidation of alcohols with alkyne groups leads to side reactions; homobenzylic alcohols are over-oxidized to respective α-ketoaldehydes; and alcohols with phenolic and chelating groups react sluggishly.

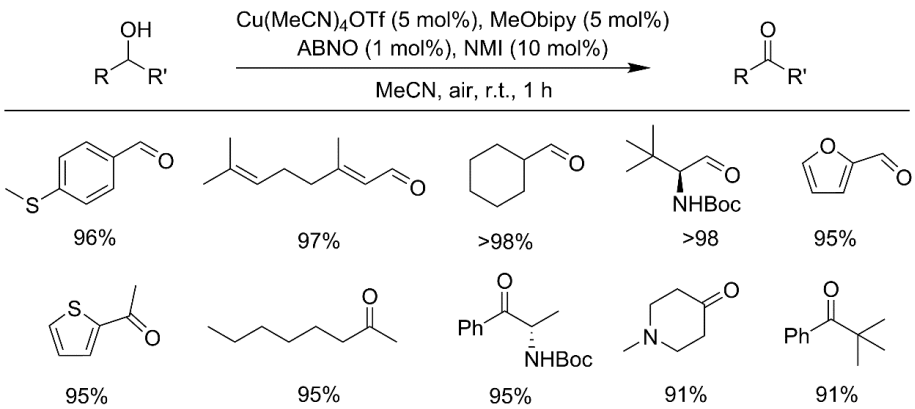


Scheme 3.3.2. Catalytic cycle for the Cu(I)/bipy/TEMPO/NMI-catalyzed aerobic oxidation of alcohols proposed by Stahl and co-workers.[60,61]



Scheme 3.3.3. Selected examples of alcohols oxidized with the Cu(I)/bipy/TEMPO/NMI catalyst system by Stahl and co-workers.[59]

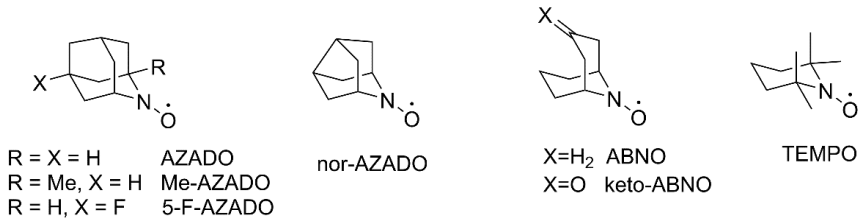
As discussed above, the catalyst systems based on the combined use of Cu(I) salts, bipy, TEMPO and NMI enable highly selective aerobic oxidation of various primary alcohols to the respective aldehydes under benign conditions. However, these catalysts perform sluggishly in oxidation of secondary alcohols to ketones. The unsatisfactory performance of these catalysts with secondary alcohols has been attributed to steric crowding around the N-O• group in TEMPO, which hampers the rate-determining α-hydride abstraction from secondary alcohols that are sterically more hindered than primary alcohols (Scheme 3.3.2, **step 6**).[60,61,76] Stahl and co-workers[76] showed that secondary alcohol oxidation rates can be significantly increased by replacing catalytic TEMPO with the sterically less hindered nitroxyl radical 9-azabicyclo[3.3.1]nonane N-oxyl (ABNO). They reported that secondary alcohols, as well as primary ones, can be readily oxidized to the respective carbonyl compounds with a Cu(I)/ABNO/bipy/NMI catalyst system within 1h under ambient conditions (Scheme 3.3.4). The reaction tolerates a variety of functionalities including sulfides, C=C bonds, carbamates, heteroaromatics and tertiary amines, but has the same limitations related to oxidation of terminal alkynes, homobenzylic alcohols, phenols and chelating substrates as reported for the Cu(I)/bipy/TEMPO/NMI system.



Scheme 3.3.4. Selected examples of carbonyl compounds and their yields obtained by Cu(I)/MeObipy/ABNO/NMI-catalyzed oxidation of alcohols by Stahl and co-workers.[76]

According to a study by Iwabuchi and coworkers,[62] a number of unhindered nitroxides, including AZADO, 5-F-AZADO, nor-AZADO, 1-Me-AZADO and keto-ABNO can be used in combination with a CuCl/bipy/DMAP catalyst system to oxidize both primary and secondary amino alcohols to corresponding aldehydes and ketones in high yields under

ambient conditions (Scheme 3.3.5). Furthermore, the authors demonstrated that the catalyst system outperforms a number of traditional alcohol oxidation methods in oxidation of aminoalcohols. For example, alcohol oxidations performed with Dess-Martin periodinane, DMSO/oxalylchloride, pyridinium chlorochromate and tetrapropylammonium perruthenate all gave lower yields of aminocarbonyl compounds than the authors obtained using aerobic oxidation with the CuCl/AZADO/bipy/DMAP catalyst. This highlights the potential of the catalyst system for oxidation of aminoalcohols that are often cumbersome to oxidize using other methods.



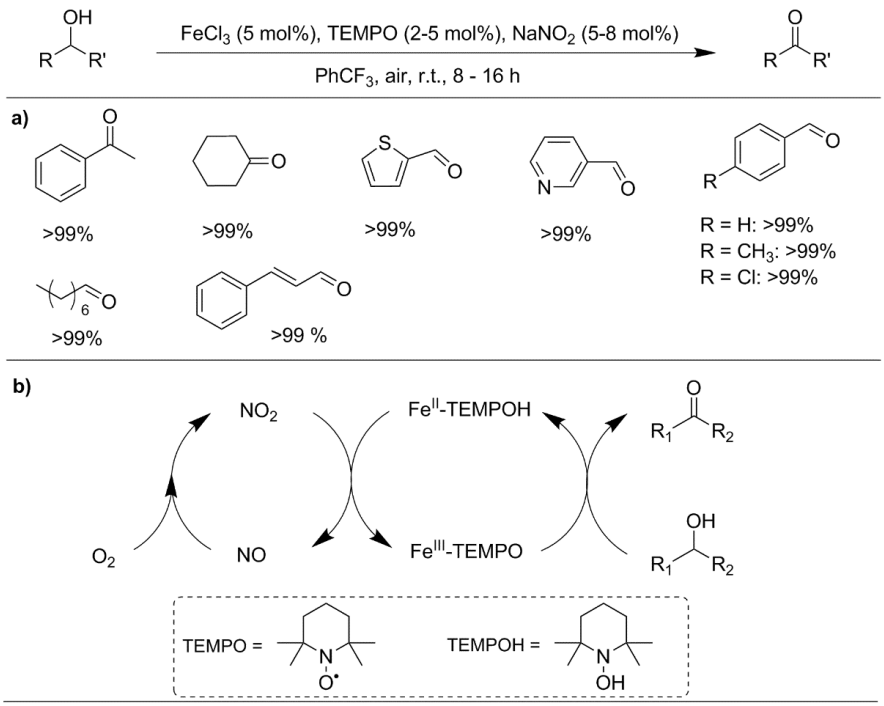
Scheme 3.3.5. Structures of nitroxyl radicals that Iwabuchi and coworkers used as co-catalysts in aerobic oxidation of alcohols.[62]

To conclude: a number of Cu/nitroxide catalyst systems have been reported for the aerobic oxidation of alcohols. Catalyst systems consisting of Cu(I) salts, nitroxides, bidentate *N,N*-donor ligands and weakly coordinating *N*-donor bases enable fast and selective oxidation of primary and secondary alcohols to the respective aldehydes and ketones under very benign conditions. Conversion of primary alcohols to aldehydes can be conducted using TEMPO as a nitroxyl radical, while oxidation of secondary alcohols to ketones requires the use of sterically less hindered nitroxides, such as ABNO, AZADO or their derivatives. These catalyst systems have been shown to have broad substrate scopes, although some limitations have also been recognized.

The use of homogenous Cu(I)/bipy/nitroxide/organic base catalysts for alcohol oxidation has lately gained popularity among synthetic chemists and ready-made catalyst solutions consisting of TEMPO/bipy/NMI and ABNO/bipy/NMI are nowadays commercially available.[77] The use of these catalyst solutions enables straightforward alcohol oxidations just by mixing the catalyst solution with the desired alcohol and Cu(I) salt and stirring the solution under open air at room temperature. These catalysts have also been proven applicable for synthesis of imines, nitriles and heterocycles from alcohols and amines.[17,78–80]

3.4 Iron co-catalysts

During recent years, aerobic alcohol oxidation catalysts based on the combined use of nitroxides and Fe-based co-catalysts have gained popularity due to their cheap price and the non-toxicity of Fe. In 2005, Liang and co-workers[81] published a seminal work in the field that described an *in situ* prepared alcohol oxidation catalyst system consisting of $FeCl_3$, TEMPO and $NaNO_2$. According to the authors, the use of this catalyst system enables selective oxidation of aliphatic, allylic, benzylic and heteroaromatic primary and secondary alcohols to aldehydes and ketones under ambient air in trifluorotoluene solution (Scheme 3.4.1a). They proposed a reaction mechanism which they termed a "*cascade of redox reactions*" involving alcohol oxidation by Fe^{III}-TEMPO complex (Scheme 3.4.1b).



Scheme 3.4.1. a) Selected examples of carbonyl compounds and their yields obtained using TEMPO/$FeCl_3$/$NaNO_2$-catalyzed aerobic oxidation of alcohols by Liang and co-workers.[81] b) The proposed reaction mechanism

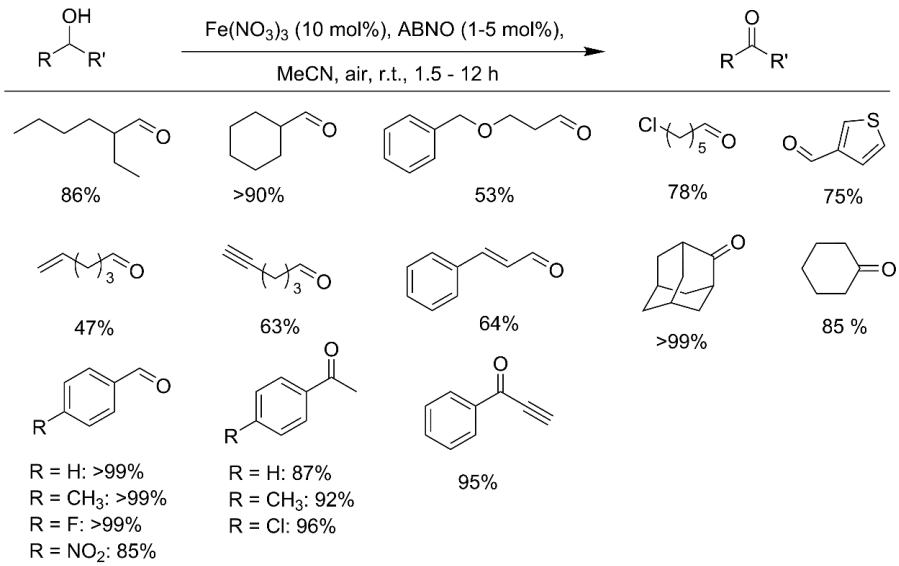
Since the publication of the $FeCl_3$/TEMPO/$NaNO_2$ system by Liang and co-workers in 2005, a few similar catalyst systems with slight modifications have been published. For example, 4-acetamido-TEMPO has been utilized as a nitroxyl radical instead of TEMPO;[82] $Fe(NO_3)_3$ has been used to replace $FeCl_3$;[83] and NaCl has been added to activate the catalyst.[84,85] These

pioneering works on Fe/nitroxide catalysis demonstrate that the selective aerobic oxidation of alcohols is possible using cheap and readily available Fe-based co-catalysts under benign conditions. However, the benefits achieved by using Fe co-catalysts are largely trumped by the mandatory use of chlorinated solvents as reaction media with the above catalysts. Luckily, methods based on non-chlorinated solvents have also been developed. For example, in 2008 Wang and Liang[86] reported that an *in situ* prepared catalyst consisting of $Fe(NO_3)_3$ and 4-OH-TEMPO can be used for the aerobic oxidation of simple allylic, benzylic and heteroaromatic primary alcohols to aldehydes in MeCN under ambient air. According to the authors, oxidation of aliphatic primary alcohols leads to partial over oxidation to carboxylic acids, which hampers the applicability of the method for oxidation of these substrates, while oxidation of allylic, benzylic and heteroaromatic primary alcohols is highly selective. It is noteworthy that the method should also be applicable for oxidation of aliphatic and benzylic secondary alcohols to the respective ketones in high yields, which is rarely reported with catalyst systems that employ TEMPO or its analogues as nitroxide catalysts.

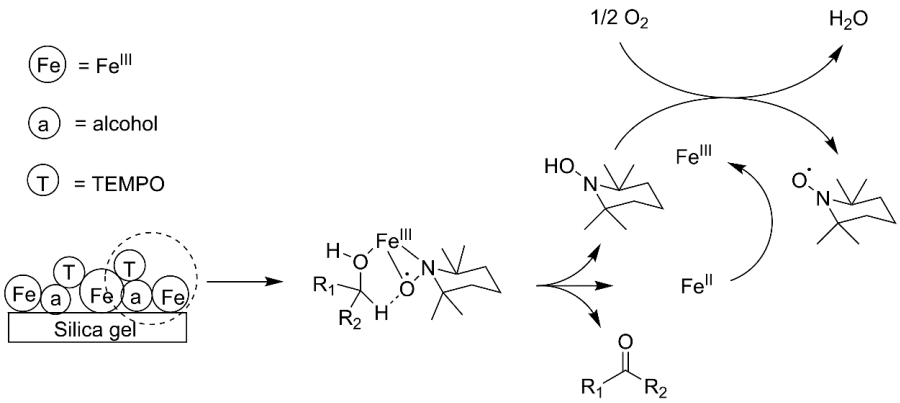
Gao and co-workers[87] showed that the efficiency of the above $Fe(NO_3)_3$/4-OH-TEMPO catalyst system can be increased by replacing 4-OH-TEMPO with sterically less hindered ABNO. This enables aerobic conversion of both primary and secondary alcohols to the respective aldehydes and ketones within 1.5–12 h reaction times, while oxidations take 10-24 h with the 4-OH-TEMPO-based catalyst. Based on substrate scope studies, the ABNO-based catalyst is compatible with aliphatic, allylic and benzylic primary and secondary alcohols (Scheme 3.4.2). Minor selectivity issues are expected with unconjugated double and triple bonds, halogens and ethers. According to brief mechanistic investigations that Gao and co-workers performed with benzylic alcohols, they suggested that the rate-determining step of the reaction is α-C-H bond cleavage that involves a carbocation transition state. The authors suggested the following mechanism: *"(1) substrate oxidation mediated by Fe(III) and ABNO via an Fe(III) alkoxide intermediate and (2) catalyst oxidation in which Fe(II) and reduced ABNO are oxidized by O_2 via NO_x generated in situ by NO_3^-."*[87]

In addition to purely homogeneous catalyst systems, partially heterogeneous Fe/nitroxide catalysts have also been developed for the aerobic oxidation of alcohols. For example, in 2012, Gao and co-workers[88] reported that a combination of TEMPO and $FeCl_3$ catalyzes the aerobic oxidation of alcohols in the presence of silica gel. The authors suggested that silica has a catalytic role as a solid adsorbent that binds TEMPO, Fe and alcohol on its surface and aids the reaction by bringing the reacting species in close proximity to each other. According to the suggested mechanism, alcohols are oxidized by an Fe^{III}-TEMPO-alkoxy intermediate, resulting in formation of carbonyl compounds and a reduced catalyst. Re-generation of Fe^{III} takes place through reaction of Fe^{II} with TEMPO. Finally, O_2 oxidizes TEMPOH to TEMPO (Scheme 3.4.3). According to the results presented in the article, the

oxidation method is suitable for oxidation of benzylic primary alcohols with a catalyst consisting of TEMPO (2-5 mol%), $FeCl_3$ (8-10 mol%) and silica gel (0.04 g / 1 mmol of alcohol) in toluene under air or O_2 (1 atm) at 80 °C. Acyclic aliphatic secondary alcohols should also be amenable to oxidation if an increased catalyst amount of 10 mol % TEMPO and 20 mol% $FeCl_3$ is used, but cyclohexanol and aliphatic primary alcohols react sluggishly.



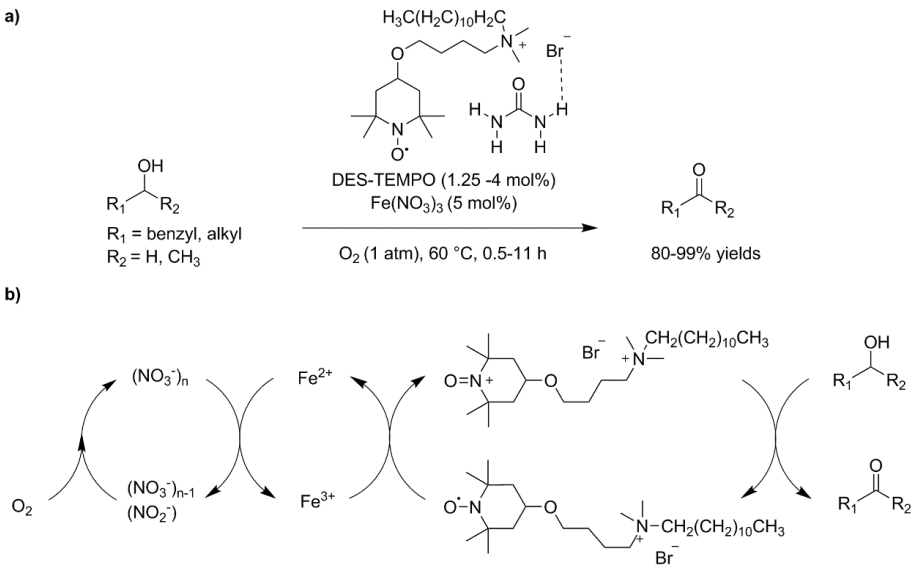
Scheme 3.4.2. Examples of carbonyl compounds and their yields, obtained by Gao and co-workers with $Fe(NO_3)_3$/ABNO-catalyzed aerobic oxidation of alcohols.[87]



Scheme 3.4.3. Mechanistic proposal for the aerobic oxidation of alcohols with TEMPO/$FeCl_3$/silica gel catalyst by Gao and co-workers.[88]

In 2013, Gao and co-workers[89] reported that the activity of the above-mentioned TEMPO/$FeCl_3$/silica gel catalyst system can be increased by covalently binding TEMPO to mesoporous SBA-15 silica and by adding a catalytic amount of $NaNO_2$ into the reaction. The use of this catalyst enables the aerobic oxidation of activated and unactivated primary and secondary alcohols to aldehydes and ketones under O_2 (1 atm) at room temperature in toluene. According to the article, the solid nitroxyl catalyst should be recyclable at least ten times without a marked decrease in catalytic activity, but fresh $NaNO_2$ has to be added after each consecutive use of the catalyst and $FeCl_3$ after every five uses.

Zhao and co-workers[90] have reported a deep eutectic solvent supported TEMPO catalyst system for the aerobic oxidation of alcohols. The catalyst consists of *N,N*-dimethyl-(4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl)dodecyl ammonium salt ([Quaternium-TEMPO]$^+$Br$^-$), urea and $Fe(NO_3)_3 \cdot 9H_2O$ (Scheme 3.4.4a). The system can be used for converting simple aliphatic and benzylic primary and secondary alcohols to aldehydes and ketones in solvent-free conditions under O_2 (1 atm) at 60 °C. Zhao and co-workers suggested a mechanism for the catalytic reaction based on pertinent literature. The suggested mechanism consists of three subsequent catalytic cycles and involves alcohol oxidation by the oxoammonium cation of [quaternium-TEMPO]$^+$Br$^-$ (Scheme 3.4.4b).



Scheme 3.4.4. a) Reaction scheme and b) suggested oxidation mechanism for deep eutectic solvent supported TEMPO-catalyzed oxidation of alcohols by Zhao and co-workers.[90]

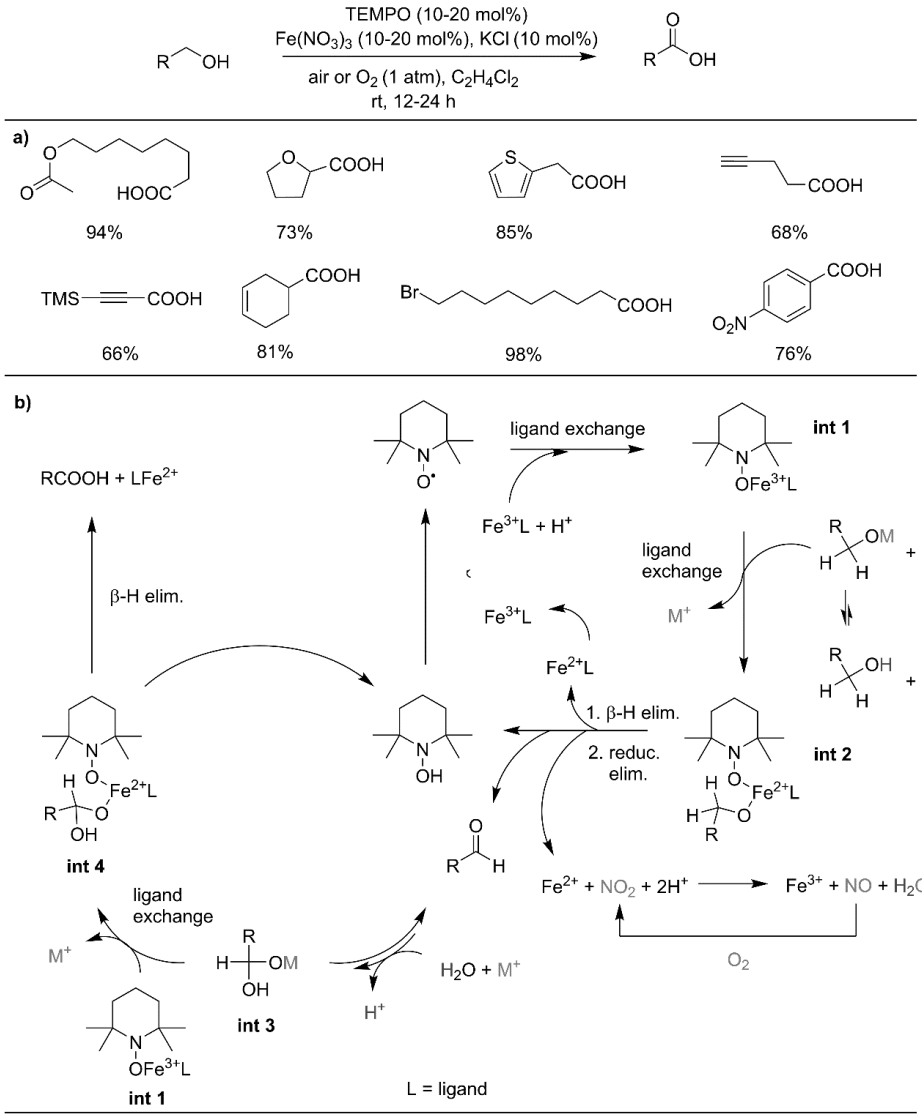
After the publication of the first nitroxide-catalyzed aerobic oxidation of primary alcohols to aldehydes by Semmelhack and co-workers[23] in 1984, over

30 years passed before the first nitroxide-based catalyst system was published that enabled selective one-step oxidation of primary alcohols to carboxylic acids. Finally, in 2016, both we[I] and Ma and co-workers[91] simultaneously published Fe/nitroxide-based catalytic methods for the aerobic oxidation of primary alcohols to carboxylic acids.

The catalyst system published by Ma and co-workers is based on the use of TEMPO, $Fe(NO_3)_3$ and KCl (10-20 mol% each) under air or pure oxygen (1 atm) in 1,2-dicholoroethane at room temperature (Scheme 3.4.5a).[91] According to the substrate scope studies presented in the article, the oxidation protocol is compatible with various functional groups, including esters, halogens, double bonds, triple bonds, silyls and heteroaromatics. They were able to convert primary alcohols bearing the above functional groups to the respective carboxylic acids in 55-99% yields within 12-24 h reaction times using 1 mmol of substrate. The method also seems to be suitable for preparative scale synthesis as a few successful alcohol oxidations with this catalyst were reported with 9-55 g substrate amounts. In addition to substrate scope studies, the article also included a mechanistic proposal, which involves coupling of TEMPO and Fe^{3+}. This leads to formation of **int 1** (Scheme 3.4.5b), which then reacts with alcohol to form **int 2** that produces the aldehyde, TEMPOH and Fe^{2+} through β-H elimination and reductive elimination. Then, Fe^{2+} is oxidized back to Fe^{3+} in a reaction with NO_2 that is converted to NO. The terminal oxidant O_2 reoxidizes NO to NO_2. TEMPOH is converted back to TEMPO in a reaction with Fe^{3+}. The oxidation of formed aldehyde to carboxylic acid is initiated by metal-assisted formation of aldehyde hydrate **int 3**, which then undergoes oxidation to carboxylic acid through similar steps as described above for the alcohol oxidation.

In our work covering the topic of Fe/nitroxide-catalyzed aerobic oxidation of alcohols, we showed that primary alcohols can be converted selectively to either aldehydes or carboxylic acids in high yields with a catalyst system consisting of TEMPO, $Fe(NO_3)_3$ and 2,2'-bipyridine (1.5-5 mol% each) in glacial AcOH using ambient air or O_2 (1 atm) as oxidant. For a detailed description of the work, see the parts concerning publication **I** in the 'Results and discussion' chapter.

In conclusion, Fe/nitroxide catalyst systems consisting of TEMPO and $Fe(NO_3)_3$ or TEMPO, FeCl and $NaNO_2$ are applicable to the selective oxidation of primary and secondary alcohols to the respective aldehydes and ketones under mild conditions. Also, oxidation of primary alcohols to the respective carboxylic acids has been demonstrated recently with Fe/nitroxide catalysts. The advantages of using Fe/nitroxide systems for the aerobic oxidation of alcohols include the cheap price of Fe salts and effortless catalyst preparation *in situ*. Considering the above benefits, Fe/nitroxide-based methods seem to be viable options for converting alcohols to carbonyl or carboxylic compounds on the laboratory scale. However, the applicability of these catalytic methods to oxidation of complex alcohols that bear functional groups in their structure remains relatively little investigated.



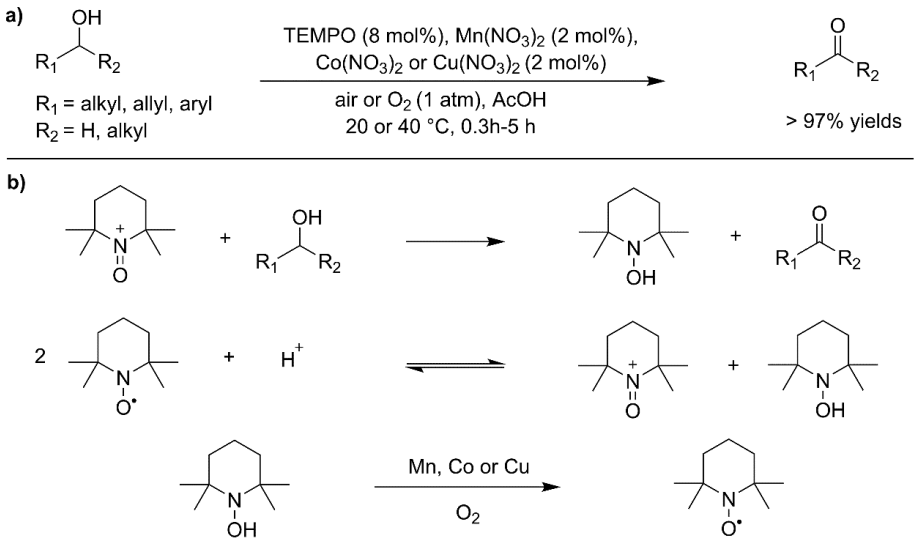
Scheme 3.4.5. a) Reaction scope and b) suggested reaction mechanism for the one-step oxidation of primary alcohols to carboxylic acids by Ma and co-workers.[91]

3.5 Other first-row transition metal co-catalysts

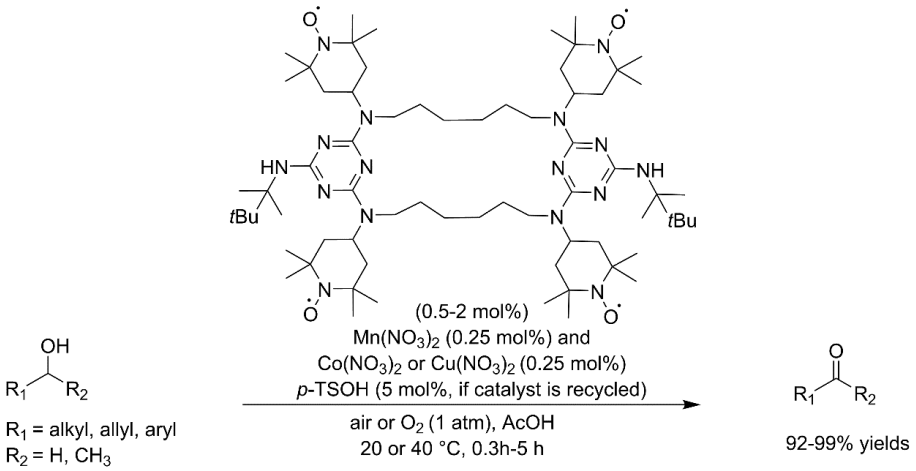
3.5.1 Cobalt and manganese

The strategy of using of Co and Mn salts as catalysts for the aerobic oxidation of alcohols has been known for more than 15 years already. In 2001, Minisci and co-workers[92] described the use of Co/Mn and Cu/Mn nitrates with TEMPO in glacial AcOH to catalyze the aerobic oxidation of alcohols to aldehydes and ketones. Interestingly, high catalyst activity was only achieved by combining either Co or Cu with Mn and TEMPO, while using any of the three metals alone resulted in poor catalytic performance. The authors reported that both primary and secondary alcohols could be converted to the respective aldehydes and ketones by utlizing bimetallic Cu/Mn/TEMPO and Co/Mn/TEMPO catalysts at 20-40 °C temperature under ambient air or O_2 (Scheme 3.5.1a). Over 95% yields were reported with simple allylic, benzylic and aliphatic substrates, but detailed functional group tolerance was not examined. However, the use of glacial AcOH as a solvent may limit the use of this method with alcohols bearing highly acid labile structures and oxidation of sulfides should be expected.[93] Experimental mechanistic studies were not included in the article but the authors suggested that alcohols are oxidized by the oxoammonium cation $TEMPO^+$, which is formed through acid catalyzed disproportionation of 2*TEMPO to TEMPOH and $TEMPO^+$. TEMPO is then regenerated through aerobic metal salt catalyzed oxidation of TEMPOH (Scheme 3.5.1b).

Soon after publication of the above method, Minisci and co-workers[94] reported a modified version of the catalyst system that is based on the use of a macrocyclic amine-funtionalized nitroxyl radical instead of TEMPO (Scheme 3.5.2). The main components of the catalyst are otherwise identical to the earlier method, but the authors recommend the use of a small amount of strong acid such as *p*-toluenesulfonic acid (*p*-TSOH) as an additive in the reaction. The role of the strong acid is to protonate the amine groups present in the nitroxide so that the catalyst can be recycled after the reaction as as follows: 1) evaporation of solvent; 2) extraction of the reaction products with organic solvent; 3) collection of the solid catalyst by filtration. The addition of the strong acid also protects the macrocyclic nitroxide from decay during the reaction. However, adding high amounts of *p*-TSOH was shown to hamper the catalyst activity.



Scheme 3.5.1. a) Reaction scheme and b) suggested mechanism for the aerobic oxidation of alcohols by Minisci and co-workers.[92]



Scheme 3.5.2. Aerobic oxidation of alcohols catalyzed by Co/Mn and Cu/Mn nitrates and macrocyclic tetrafunctional nitroxide, developed by Minisci and co-workers.[94]

In 2005 and 2006, Baucherel and co-workers[95,96] reported that polymer-bound TEMPO can be used as a nitroxide in catalytic alcohol oxidation reactions under similar conditions as reported by Minisci and co-workers earlier.

Six years after Baucherel's first publication Yang and co-workers[97] discovered that a single metal $Co(NO_3)_2$/TEMPO can be used as an aerobic alcohol oxidation catalyst when the dimethylglyoxime ligand is utilized to

activate the metal. The catalyst system facilitates the conversion of simple benzylic, allylic and aliphatic alcohols to respective carbonyl compounds under 4 bars of O_2 at 70 °C in dichloromethane solution.

After publication of the above Co/TEMPO-based system by Yang and co-workers in 2011, the use of Mn/nitroxide or Co/nitroxide catalysts for the aerobic oxidation of alcohols has attracted little attention, while other approaches, including Cu/nitroxide, Fe/nitroxide and transition-metal-free NO_x systems have gained more research scrutiny. Due to limited interest in the topic, some central aspects related to these catalysts remained unconsidered for years. For example, the strategy of using organic ligands to activate Mn-based catalysts had not been implemented and extensive substrate scope studies had not been performed prior to our works on the topic, which were published in 2017 and 2018.[II, III] For a detailed description of our work in this area, see the parts concerning publications **II** and **III** in the 'Results and discussion' chapter.

3.5.2 Vanadium

In 1999, Kirihara and co-workers[98] reported that $VOCl_3$ catalyzes the aerobic oxidation of α-hydroxycarbonyls to α-dicarbonyl compounds. Since then, a number of V-based aerobic alcohol oxidation protocols have emerged, mainly for the oxidation of α-hydroxycarbonyls[99–102] and other activated alcohols, such as allylic,[103] benzylic[104–107] and propargylic[108–110] ones; but methods suitable for oxidation of unactivated aliphatic alcohols[111,112] have also been reported. The above systems mediate the aerobic oxidation of alcohols in the absence of nitroxides, but a few methods that utilize nitroxides as co-catalysts have been reported as well. For example, Neumann and co-workers[113] used a combination of $H_5PV_2MO_{10}O_{40}$ (1 mol%) and TEMPO (3 mol%) to oxidize primary and secondary alcohols to aldehydes and ketones under 2 bar of O_2 at 100 °C in acetone. The method was later applied in an industrial scale by DSM.[114]

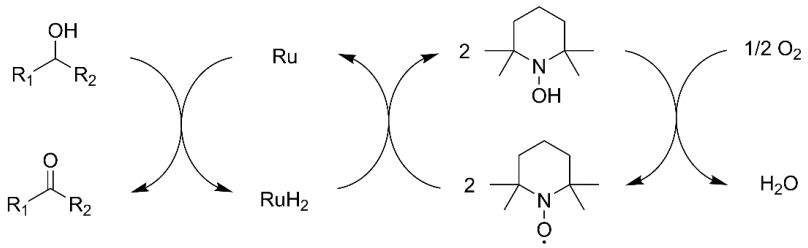
Another example of combined use of V and nitroxides dates back to 2010, when Xu and co-workers[115] reported the use of $VOSO_4$ (4 mol%) and TEMPO (4 mol%) as an aerobic alcohol oxidation catalyst under 4 bar of O_2 at 80 °C in MeCN. Based on the substrate scope studies presented in the article, the system is efficient for oxidation of benzylic primary alcohols to the respective aldehydes.

3.5.3 Ruthenium

As the oxidation of alcohol to carbonyl compound is essentially a transfer of H_2 from substrate to oxidant, it is not surprising that the traditional hydrogenation and dehydrogenation catalysts, such as Ru, have been employed to catalyze the aerobic oxidation of alcohols.[25] Most of the Ru-based aerobic oxidation systems are based on the use simple Ru salts, such as

$RuCl_3 \cdot nH_2O$, or complexes like $Ru_3O(O_2CR)_6L_n$ (where R = CH_3 or C_2H_5; L = H_2O or PPh_3) as a catalyst in the absence of nitroxides.[116,117] Although the presence of nitroxides is not requisite for achieving reactivity with Ru-based catalysts, some reports on the combined use of Ru and nitroxdes exist. For example, Sheldon and co-workers[118,119] have reported that the presence of TEMPO increases the activity of $RuCl_2(PPh_3)_3$ as an alcohol oxidation catalyst. They suggested that the reaction proceeds with a metal hydride mechanism, involving a Ru/RuH_2 pair as alcohol dehydrogenating agent and a TEMPO/TEMPOH pair as a hydrogen transfer mediator that converts O_2 to water (Scheme 3.5.3). The authors used the above catalyst to oxidize simple benzylic and aliphatic primary and secondary alcohols to aldehydes and ketones under 10 bar of O_2:N_2 (8:92) at 100 °C in chlorobenzene.

After the publication of the above described method by Sheldon and co-workers, the topic of Ru-catalyzed aerobic oxidation of alcohols has remained actively investigated, but the use of nitroxides as co-catalysts has not attracted much attention. More popular approaches include the use of Ru-based homogeneous and heterogeneous catalysts in nitroxide-free conditions.[120–125]



Scheme 3.5.3. Mechanistic proposal for $RuCl_2(PPh_3)_3$/TEMPO-catalyzed aerobic oxidation of alcohols by Sheldon and co-workers.[119]

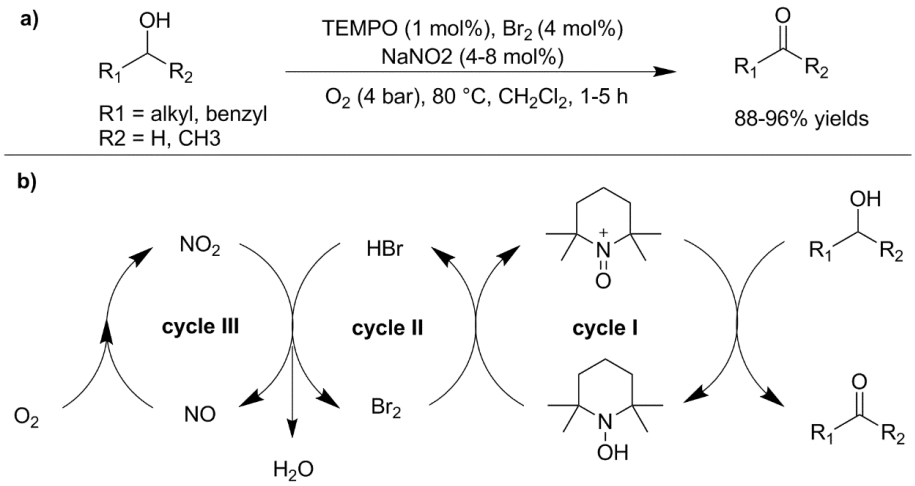
3.6 Transition-metal-free NO_x co-catalyst systems

Despite their high activities, aerobic alcohol oxidation catalysts that are based on the use of transition metals suffer from a number of drawbacks. For example, chelating substrates may bind to the metal center and diminish catalytic activity and traces of toxic metals might prevent the use of reaction products in food and drug applications.[126] Moreover, water, the ultimate green solvent, can only seldom be used as reaction media for transition-metal-catalyzed reactions, because it tends to deactivate the catalysts by displacing the substrates or intermediates from the coordination sphere of the transition metal catalysts.[127] Therefore, research on the transition-metal-free nitroxide-catalyzed aerobic oxidation of alcohols has gathered growing interest lately.[128–143] These catalyst systems generally rely on the use of nitrogen

oxides (NO_x) as oxygen activating co-catalysts. Many of the early methods also employ additional halide co-catalysts, such as bromine, hypoboromous acid or nitrosyl chloride.

The seminal publication in the field of transition-metal-free aerobic alcohol oxidation was published by Hu and co-workers[128] in 2004. The article described the use of a TEMPO/Br_2/$NaNO_2$ (1/4/4-8 mol%) catalyst system for the aerobic oxidation of alcohols under 4 bar of O_2 at 80 °C in 1,2-dicholoethane (Scheme 3.6.1a). Based on the results presented in the article, the method can be used for oxidation of simple aliphatic and benzylic alcohols to the respective aldehydes and ketones in over 90% yields. However, selectivity issues might occur with substrates bearing structures that are prone to halogenation. For example, oxidation of 2-thiophenemethanol and 3-methyl-2-buten-1-ol led to hydrobromination of the C=C bonds in the authors' hands. Also, substrates bearing basic functionalities might not be compatible with the system due to neutralization of the catalytic intermediate HBr, which leads to severely hampered reactivity, according to the article. The authors postulated a mechanism, which involves alcohol oxidation by an oxoammonium cation (Scheme 3.6.1b, **cycle I**), regeneration of the reduced nitroxide TEMPOH by Br_2 (**cycle II**) and reduction of HBr by NO_2, which is then regenerated by O_2 (**cycle III**).

Soon after publication of the original TEMPO/Br_2/$NaNO_2$ catalyst system in 2004, Hu and Co-workers[129] reported a modified version of the catalyst that utilizes 1,3-dibromo-5,5-dimethylhydantoin as a halogen source instead of hazardous Br_2 and therefore makes the method more safer to use.



Scheme 3.6.1. a) Reaction scheme and b) mechanistic proposal for the transition-metal-free aerobic alcohol oxidation by Hu and co-workers.[128]

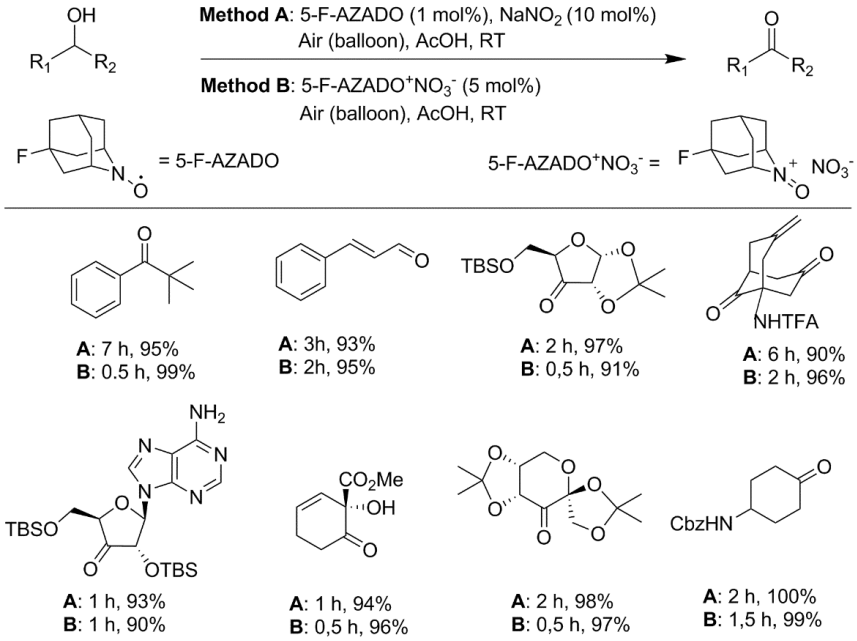
In 2007, Hu and co-workers[136] reported that very high turnover numbers (up to 16 000) can be achieved when *tert*-butyl nitrite (TBN) is used as a nitrate source in the aerobic oxidation of alcohols with a TEMPO/HBr catalyst system. In their article, the authors noted that quantitative conversion of benzylic primary alcohols to the respective aldehydes can be achieved with catalyst amounts as low as of 0.1/0.4/0.4 mol% of TEMPO/HBr/TBN under 6 bar of O_2 at 80 °C in solvent-free conditions. Increased catalyst amounts of 0.1/4/4 - 2/4/4 mol% of TEMPO/HBr/TBN are required for oxidation of aliphatic and heteroaromatic primary alcohols, as well as for oxidation of aliphatic and benzylic secondary alcohols to the corresponding carbonyl compounds.

In 2008, Liang and co-workers[137] reported a TEMPO/HCl/$NaNO_2$ catalyst system that enables aerobic oxidation of simple aliphatic, allylic and heteroaromatic primary and secondary alcohols to aldehydes and ketones under open air at room temperature. The use of ambient reaction conditions simplifies the reaction set-up remarkably compared to the above-discussed systems, as no O_2 cylinders or expensive teflon-lined autoclaves are needed when running the reactions under open air instead of high pressures of pure O_2. However, relatively large catalyst loadings (3/10/5 - 8/16/8 mol% of TEMPO/HCl/$NaNO_2$) are required to achieve sufficient reactivity under ambient conditions.

The above-described catalytic methodologies provided significant developments in the field of transition-metal-free aerobic alcohol oxidation, but the systems discussed up to this point have a few key limitations as they require the use of one or more of the following: halogenated solvents; expensive teflon-lined autoclaves; or halide catalysts that decrease reaction selectivity with substrates bearing C=C bonds. Furthermore, applicability of TEMPO/NO_x/halide-based catalysts systems seems to be limited to oxidation of simple aliphatic, allylic, benzylic and heteroaromatic alcohols, as oxidation of substrates bearing functional groups other than hydroxyls has been scarcely demonstrated with these catalysts.

In 2011, Iwabuchi and co-workers[130] introduced a halide-free alcohol oxidation catalyst that is not constrained by use of halogenated solvents or expensive autoclaves. Their method is based on the combined use of 5-F-AZADO nitroxide with $NaNO_2$ as a catalyst. The authors showed that the 5-F-AZADO/$NaNO_2$ (1/10 mol%) catalyst system can be used for oxidation of both primary and secondary alcohols to the respective aldehydes and ketones under open air at ambient temperature. Moreover, the catalytic system is compatible with various bulky and reactive functional groups and reactions are conducted in AcOH instead of chlorinated solvents (Scheme 3.6.3). Under these unforcing conditions, virtually all types of alcohols should be amenable to oxidation within a few hours. The authors suggested that the exceptionally high alcohol oxidation activity was achieved with the 5-F-AZADO/$NaNO_2$ catalyst because the utilized nitroxide is sterically accessible around the N-O·

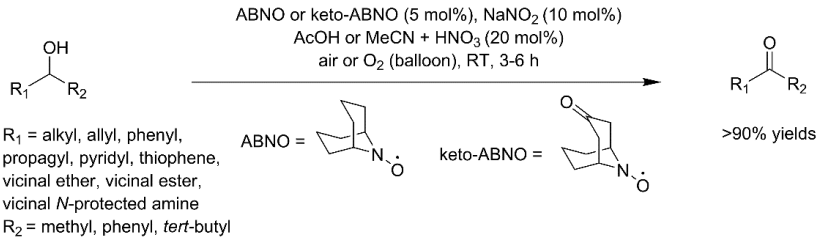
center and has a high oxidation potential of +413 mV (for comparison, the oxidation potential of TEMPO is +294 mV).[130]



Scheme 3.6.3. 5-F-AZADO/NO_x-catalyzed aerobic oxidation of alcohols and selected examples of the carbonyl compounds produced by Iwabuchi and co-workers. Oxidation method, reaction time, yield.[130]

In 2013, Lauber and Stahl[133] compared activities of various bicyclic nitroxides to that of TEMPO as a catalyst for the aerobic oxidation of secondary alcohols. As a general trend, sterically accessible bicyclic nitroxides showed significantly higher catalytic activities than TEMPO. Interestingly, the authors did not find correlation between catalytic activity and oxidation potential of the nitroxides. Instead, they suggested that some bicyclic nitroxides were catalytically more active than others due to their higher stabilities. The best results were achieved with ABNO, keto-ABNO and AZADO nitroxides. Reaction optimization and substrate scope studies were performed using ABNO and keto-ABNO nitroxides instead of AZADO because the former are significantly easier to synthesize; ABNO and its analogues can be obtained through 2-3 step syntheses from commercially available starting materials while nitroxides bearing AZADO structures require 5-10 synthetic steps. The use of an ABNO/$NaNO_2$ catalyst system enabled the aerobic oxidation of secondary alcohols to desired ketones in excellent yields under open air or O_2 (1 atm) in AcOH or MeCN+HNO_3 solutions within 3-6 h. The substrate scope was

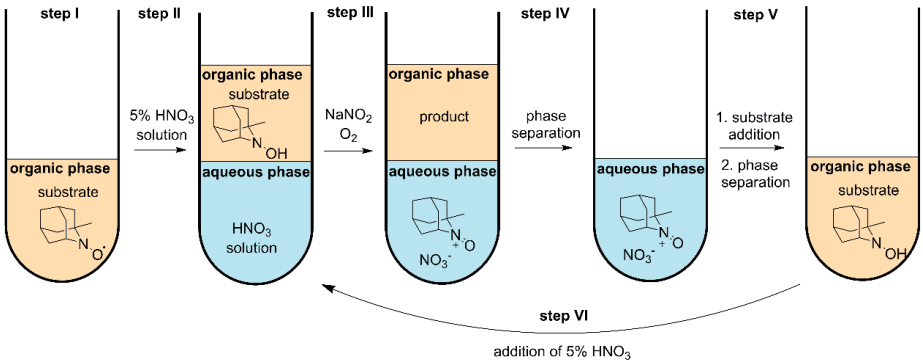
demonstrated by successful oxidation of alcohols bearing various structures and functional groups, including heteroaromatics, C-C double and triple bonds, esters, ethers, protected amines and protected alcohols. Some limitations were also emphasized. For example, the oxidation of alcohols bearing aniline structures led to the formation of diazo compounds. Also, alcohols containing tertiary amines failed to produce the desired carbonyl compounds in high yields, which was suggestedly caused by interference of these substrates with the acid-induced NO_x redox cycle.



Scheme 3.6.4. Aerobic alcohol oxidation with ABNO and keto-ABNO nitroxides by Lauber and Stahl.[133]

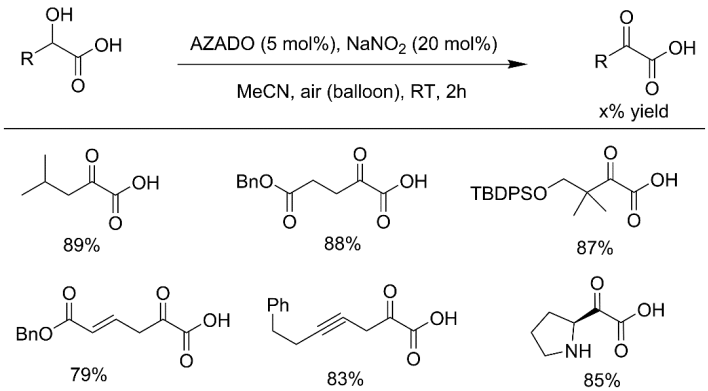
In the above-discussed study, Lauber and Stahl used cyclic voltammetry to oxidize and reduce different nitroxides and visually analyzed the symmetries of the obtained voltammograms to draw conclusions about the nitroxide stabilities. Based on these measurements and the results obtained from catalytic alcohol oxidation studies, they suggested that ABNO should not undergo significant degradation under catalytic alcohol oxidation conditions. Kakimoto and co-workers[134] came to a different conclusion about ABNO's stability in their publication concerning nitroxide stabilities. In that study, TEMPO, ABNO and 1-Me-AZADO were dissolved in dilute aqueous HNO_3, which led to instantaneous oxidation of the nitroxides to the respective oxoammonium cations by NO_x. The compositions of these solutions were then followed with UV-vis over time. The measurements showed that TEMPO and 1-Me-AZADO were stable during the whole 67 h observation period while ABNO decayed almost completely during the experiment. Based on these results, the authors noted that 1-Me-AZADO provides an optimal combination of high reactivity and sufficient stability to be employed as an alcohol oxidation catalyst, while TEMPO is stable but reacts sluggishly and ABNO is reactive but unstable. Upon finding the suitable nitroxide, Kakimoto and co-workers showed that simple aliphatic, benzylic and heteroaromatic alcohols can be oxidized using a 1-Me-AZADO/$NaNO_2$/HNO_3 (0.5/10/10 mol%) catalyst system under O_2 (balloon) at 40 °C in a two-phase system consisting of aqueous phase and water immiscible alcohol as the organic phase.[134] When they conducted the reactions under these conditions, they were able to recover and reuse the nitroxide catalyst for eight consecutive times according to the following five step procedure (Scheme 3.6.5). The organic phase, consisting on

water immiscible alcohol and 1-Me-AZADO is loaded into open reaction vessel (**step I**). Nitric acid is then added, which results in oxidation of 1-Me-AZADO to the respective oxoammonium cation 1-Me-AZADO$^+$. The oxoammonium cation instantly reacts with alcohol and produces the respective hydroxylamine 1-Me-AZADOH, which is transferred to organic phase (water immiscible alcohol) due to its lipophilic nature (**step II**). Catalytic reaction is then initiated by letting O_2 into the reaction vessel and adding $NaNO_2$ (**step III**). After completion of the reaction, the nitroxide catalyst exists in its oxoammonium form 1-Me-AZADO$^+$ in aqeous phase. The aldehyde product is isolated by decanting (**step IV**). A new batch of alcohol substrate is added over the catalyst containing aqeous phase and the reaction vessel is then shaked. This reduces oxoammonium ion to to hydroxyamine, which is then transferred to the substrate phase as a result of the altered solubility (**step V**). Subsequent removal of the aqueous phase and nitric acid addition re-activates the catalyst for second alcohol oxidation run (**step VI**).



Scheme 3.6.5. Aerobic alcohol oxidation under two-phase conditions and recycling of 1-Me-AZADO using phase separation by Kakimoto and co-workers.

In 2016, Shibuya and co-workers[135] demonstrated that an AZADO/$NaNO_2$ (5/20 mol%) catalyst can be used for the selective oxidation of α-hydroxy acids to α-keto acids under air (balloon) at room temperature in MeCN (Scheme 3.6.6). They reported over 70% product yields, which is a remarkable achievement since α-keto acids are prone to decarbonylation and their synthesis is often cumbersome through other routes.[144–146]



Scheme 3.6.6. Aerobic oxidation of α-hydroxy acids to α-keto acids by Shibuya and co-workers.[135]

In conclusion, synthesis of simple aliphatic, allylic or benzylic aldehydes can be conducted from the respective primary alcohols using transition-metal-free catalyst systems that are based on a combination of TEMPO, NO_2^- and a halogen source, such as Br_2, or HBr. Oxidations performed with the above catalysts can be conducted under neutral conditions, but the use of halogenated solvents and pure O_2 (≥1 bar) as oxidant seems to be mandatory if quantitative substrate conversions are sought. Increased catalytic activity can be obtained by conducting reactions under acidic conditions and replacing TEMPO with a sterically less hindered nitroxide, such as AZADO, ABNO or their derivative. When sterically accessible nitroxides are used and reactions are conducted in acidic media, the halide co-catalysts can be left out and reactions can be performed in non-halogenated solvents, such as AcOH or $MeCN/HNO_3$. Furthermore, ambient air seems to be a sufficient source of oxidant when halide-free $NaNO_2$/nitroxide catalysts are used and these catalysts seem to be compatible with virtually all classes of substrates, including aliphatic, allylic, benzylic and heteroaromatic primary and secondary alcohols. So far, clear limitations on substrate scope have only been recognized with alcohols bearing aniline structures and tertiary amines, which seem to cause selectivity issues and/or low conversions with $NaNO_2$/nitroxide catalysts.

4 Results and discussion

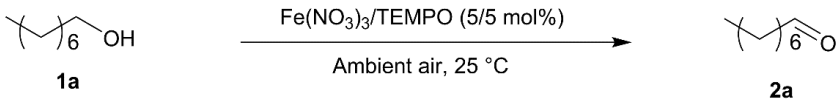
4.1 Experimental notes

Detailed information considering experimental procedures and data acquisition can be found in the attached publications **I-III** and in the related supporting material that is available on the publishers' webpages. Each synthesized compound was given a product number in the attached publications and the same numbering is used in the following chapters.

4.2 Iron/nitroxide catalyst system (publication I)

The study on Fe/nitroxide-catalyzed alcohol oxidation was inititated by performing oxidation of 1-octanol (**1a**) to octanal (**2a**) with a known catalyst system consisting of TEMPO and $Fe(NO_3)_3$ (5 mol% of both, compared to alcohol).[86] The reaction was conducted in MeCN solution, under ambient air in an open test tube, which resulted in low 46% **1a** conversion and 45% **2a** yield, despite the long reaction time of 23 h (Table 4.2.1, entry 1). To increase the reaction efficiency, screening of other Fe salts, reaction solvents and addition of different organic ligands was attempted. These experiments revealed that substrate conversion and product yield could be significantly increased by changing the reaction solvent from MeCN to glacial AcOH and by adding the 2,2'-bipyridine (bipy) (5 mol%) ligand into the reaction (entry 2). Changing the solvent or adding the ligand alone did not result in similarly increased reactivity (entries 3-4). Various other generally used solvents and organic ligands were also screened, but found to be less efficient. The use of Fe salts with other counter anions than NO_3^- resulted in negligible substrate conversion, which highlights the role of NO_3^- in the reaction.

Table 4.2.1. *Aerobic oxidation of 1-octanol to octanal.*[a]



1a **2a**

Entry	Ligand	Solvent	Time [h]	Conversion [%]	Yield [%]
1	-	MeCN	23	46	45
2	bipy	AcOH	6	98	96
3	-	AcOH	23	49	48
4	bipy	MeCN	23	30	29

[a] Conversions and yields determined with GC-FID using acetophenone as internal standard.

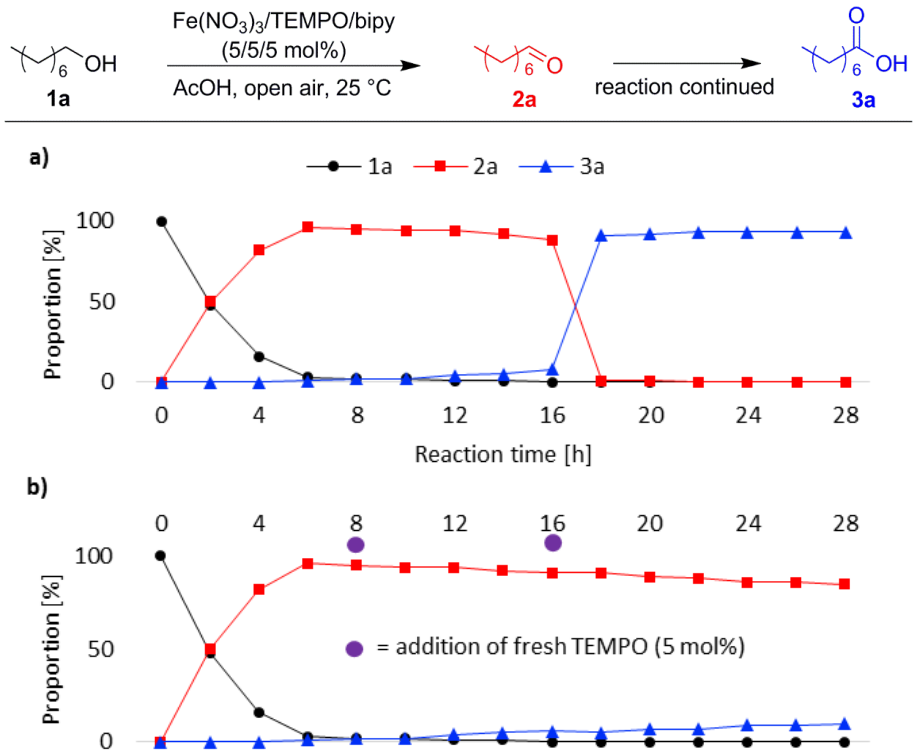
As a combination of $Fe(NO_3)_3$/bipy/TEMPO showed the highest activity in the oxidation of **1a** to **2a**, this catalyst system was studied in more detail. The investigations revealed that **2a** was further oxidized to octanoic acid (**3a**) in 93 % yield when the reaction time was extended from 6 to 23 h. This was a surprising finding as TEMPO and other nitroxides are known to inhibit the aerobic oxidation of aldehydes to carboxylic acids and one-step oxidation of primary alcohols to carboxylic acids had not been reported with nitroxide-based catalysts at the time of this work. To see how the oxidation of alcohol to aldehyde and subsequent conversion of aldehyde to carboxylic acid progressed during **1a** oxidation, the reaction was followed by taking samples for GC-analysis. The analysis revealed that the oxidation of alcohol **1a** to aldehyde **2a** and further to carboxylic acid **3a** took place in a stepwise manner (Scheme 4.2.1a). During the first 6 h of the reaction, **1a** was oxidized to **2a** while further oxidation to **3a** was negligible. Conversion of **1a** to **2a** was followed by a 10 h 'resting' period during which aldehyde **2a** was the dominant component in the reaction while the concentration of carboxylic acid **3a** remained very low. Finally, after 16 h, **2a** was suddenly oxidized to **3a**. It was reasoned that the rapid oxidation of aldehyde **2a** might have resulted from quenching of TEMPO, which would have then allowed the auto-oxidation of the aldehyde **2a** to the carboxylic acid **3a**.[147,148] The hypothesis was confirmed by GC analysis, which showed that the TEMPO concentration steadily decreased during the reaction and eventually fell below the detection limit at around 16 h time. Furthermore, gradual addition of TEMPO (5 mol%) into the reaction every 8 h prohibited the oxidation of the formed aldehyde **2a** to carboxylic acid **3a** (Figure 4.2.1b), which further supports the proposed auto-oxidation mechanism.

The effect of the $Fe(NO_3)_3$/bipy catalyst on aldehyde oxidation was studied in the absence of TEMPO (Figure 4.2). The experiment conducted in the presence of 5 mol% of $Fe(NO_3)_3$/bipy resulted in quantitative oxidation of the aldehyde **2a** to carboxylic acid **3a** within 1 h (Figure 4.2.2a), while the oxidation took 12 h in the absence of $Fe(NO_3)_3$/bipy (Figure 4.2.2b). This shows that $Fe(NO_3)_3$/bipy catalyzes the oxidation of aldehydes to carboxylic acids if TEMPO is not present, and therefore explains why aldehyde **2a** was rapidly converted to carboxylic acid **3a** after complete degradation of TEMPO during the catalytic oxidation of **1a**.

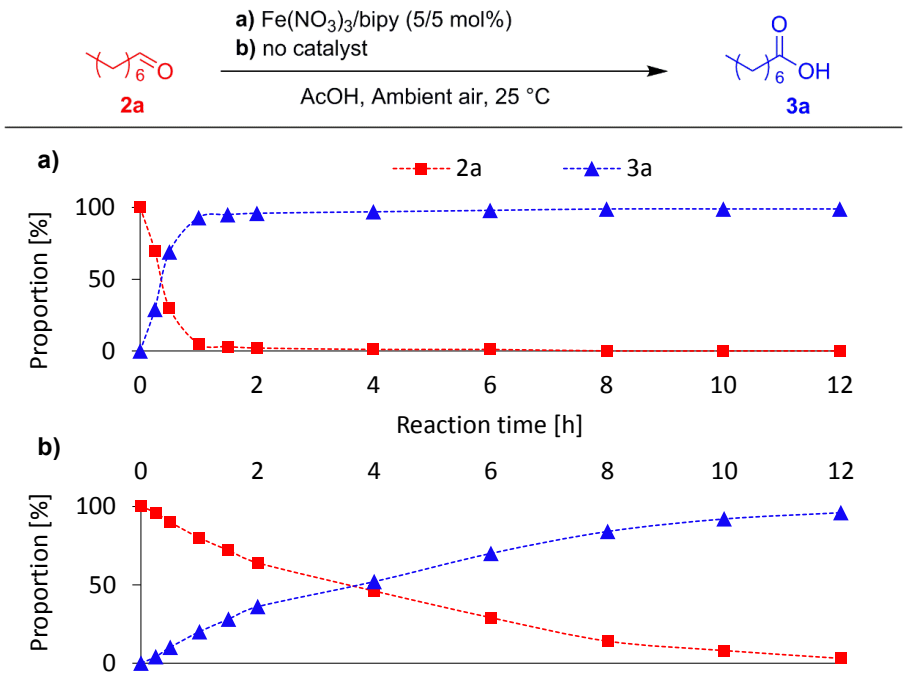
Substrate scope studies conducted with the $Fe(NO_3)_3$/bipy/TEMPO catalyst showed that the method is compatible with various aliphatic alcohols containing different structures and functional groups (Table 4.2.2). For example, alcohols bearing aromatic side chains (substrate **1b**) halogens (**1c**), double bonds (**1d**), triple bonds (**1e**), ethers (**1f**) and diols (**1g**) could be selectively oxidized either to aldehydes or further to carboxylic acids under the same ambient conditions that were optimized for **1a**. Oxidation of secondary alcohols **1h**-**1j** was also attempted with the $Fe(NO_3)_3$/bipy/TEMPO catalyst system, but only incomplete substrate conversions were achieved. The reactivity issue with secondary alcohols was overcome by replacing catalytic

TEMPO with the sterically less hindered nitroxyl radical ABNO. This resulted in significantly improved catalytic performance and secondary alcohols **1h-1j** were smoothly converted to the respective ketones **2h-2j** with ≥99% yields within a few hours.

Oxidation of benzylic, allylic and heteroaromatic primary alcohols (Table 4.2.3, substrates **1k-1t**) was conducted using 1.5 mol% loading of the $Fe(NO_3)_3$/bipy/TEMPO catalyst under pure O_2 (1 atm) at 80 °C. Under these conditions, benzylic and allylic primary alcohols were converted selectively to either aldehydes (**2k-2p**) or carboxylic acids (**3k-3p**) within just a few hours. Heteroaromatic alcohols (**1q-1t**) were selectively oxidized to the corresponding aldehydes (**2q-2t**), but further oxidation to the respective carboxylic acids could not be achieved.

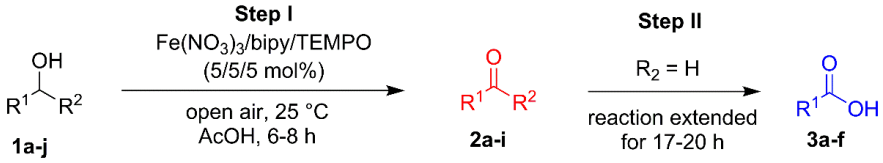


Scheme 4.2.1. Catalytic oxidation of 1-octanol with a) $Fe(NO_3)_3$/TEMPO/bipy (5/5/5 mol%) catalyst; b) catalyst loading 5/15/5 mol%, TEMPO added in three steps at 0 h, 8 h and 16 h. Yields determined with GC-FID using acetophenone as internal standard.



Scheme 4.2.2. . Aerobic oxidation of octanal with a) $Fe(NO_3)_3$/bipy (5/5 mol%) catalyst; b) no catalyst. Yields determined with GC-FID using acetophenone as internal standard.

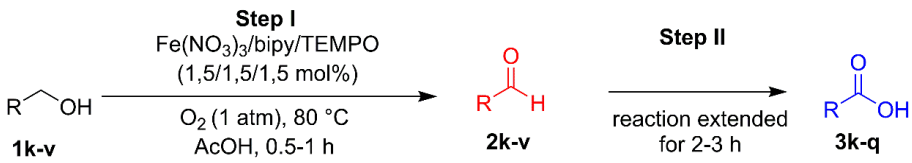
Table 4.2.2. *Aerobic oxidation of aliphatic alcohols with the $Fe(NO_3)_3$/bipy/TEMPO catalyst system.*



Substrate	Step I product	Step I yield[b] (conv.) [%]	Step II product	Step II yield[b] (conv.) [%]
1a	**2a**	96 (97)	**3a**	93 (>99)
1b	**2b**	93 (99)	**3b**	89 (95)
1c	**2c**	90 (92)	**3c**	86 (94)
1d	**2d**	94 (>99)	**3d**	89 (98)
1e	**2e**	85 (98)	**3e**	76 (>99)
1f	**2f**	89 (99)	**3f**	73 (96)
1g	-	-	**3g**	62 (99)
1h	**2h**	>99 (>99)[a]		
1i	**2i**	99 (>99)[a]		
1j	**2j**	99 (>99)[a]		

[a] ABNO used instead of TEMPO. [b] Yield and conversion of alcohol is presented for aldehyde and ketone products, conversion of aldehyde is presented for carboxylic acid products. Yields determined with GC-FID using acetophenone as internal standard.

Table 4.2.3. *Aerobic oxidation of activated alcohols with $Fe(NO_3)_3$/bipy/TEMPO catalyst system.*



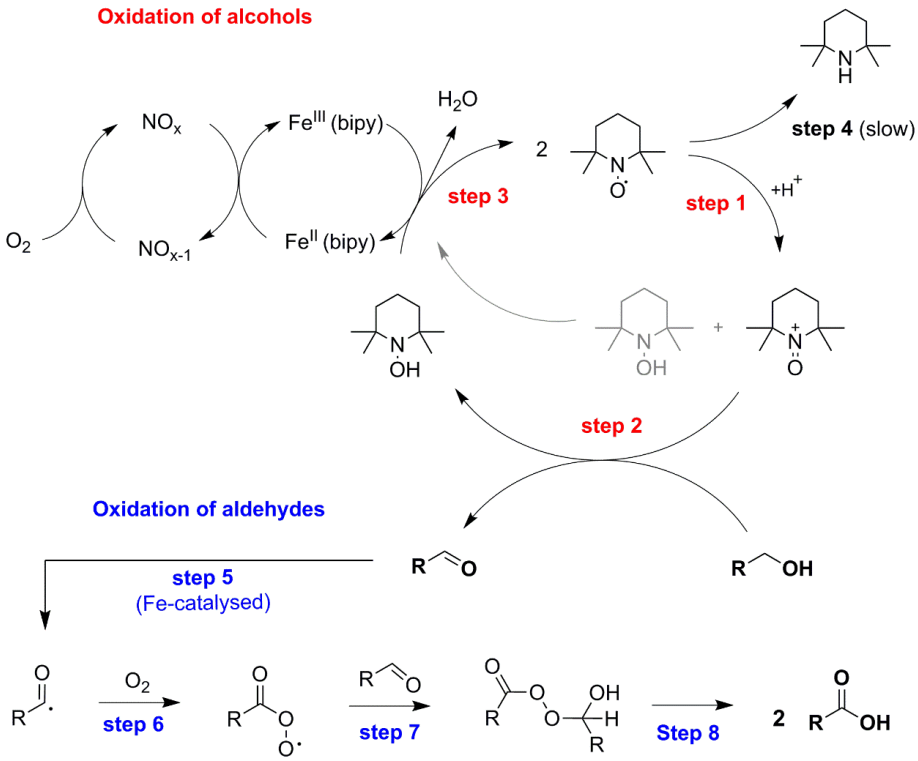
Substrate	Step I product	Step I yield[a] (conv.) [%]	Step II product	Step II yield[a] (conv.) [%]
1k	**2k**	>99 (>99)	**2k**	86 (89)
1l	**2l**	>99 (>99)	**2l**	78 (81)
1m	**2m**	99 (>99)	**2m**	76 (78)
1n	**2n**	>99 (>99)	**2n**	91 (93)
1o	**2o**	99 (>99)	**2o**	81 (84)
1p	**2p**	96 (>99)	**2p**	60 (65)
1q	**2q**	>99 (>99)	-	- (<5)
1r	**2r**	>99 (>99)	-	- (<5)
1s	**2s**	92 (96)	-	- (<5)
1t	**2t**	82 (95)	-	-

[a] Yield and conversion of alcohol is presented for aldehyde and ketone products, conversion of aldehyde is presented for carboxylic acid products. Yields determined with GC-FID using acetophenone as internal standard.

Based on experimental studies and pertinent literature, the following mechanism was suggested for the catalytic oxidation of alcohols with the $Fe(NO_3)_3$/bipy/TEMPO catalyst system. The reaction is initiated by acid-induced disproportionation of TEMPO to a hydroxylamine (TEMPOH) and an oxoammonium cation ($TEMPO^+$) (Scheme 4.2.3, **step 1**).[39,40,149] $TEMPO^+$ reacts with the alcohol and produces TEMPOH and aldehyde (**Step 2**).[36,90,94] TEMPOH is oxidized back to TEMPO by the Fe^{III}[bipy] complex, which itself is reduced to Fe^{II}[bipy] (**step 3**).[90,150] Regeneration of Fe^{III}[bipy] takes place through reaction of Fe^{II}[bipy] with an oxidizing NO_x species. The latter is formed from NO_3^- under the acidic reaction conditions in the presence of O_2.[90,151,152] The alcohol oxidation cycle is closed by aerobic conversion of

reduced NO_x back to an oxidized state by O_2.[90,150,152] Together, the above reactions form a cascade of redox reactions that propels the oxidation of primary alcohols to aldehydes and produces water as a side product. Further oxidation of the formed aldehydes is inhibited as long as radical scavenging TEMPO is present in the reaction. However, slow degradation of TEMPO (**step 4**) eventually leads to initiation of Fe(bipy)-catalyzed auto-oxidation of the aldehyde which produces carboxylic acid as the final product (**steps 5-8**).[147,153–156]

To conclude: the study shows that highly selective one-step oxidation of aliphatic and benzylic primary alcohols to either aldehydes or carboxylic acids can be achieved under benign conditions using an *in situ* prepared $Fe(NO_3)_3$/bipy/TEMPO catalyst. The catalyst system is compatible with a wide range of functionalities, including C-C double bonds and triple bonds, ethers, esters and halogens. The method can also be applied to the selective oxidation of secondary alcohols to ketones by replacing the catalytic TEMPO with sterically less encumbered nitroxide ABNO.

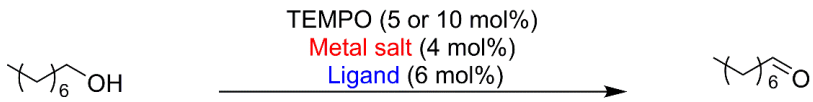


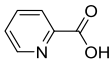
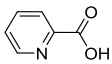
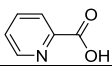
Scheme 4.3. Proposed mechanism for the aerobic oxidation of primary alcohols to aldehydes and further to carboxylic acids.

4.3 Manganese/nitroxide catalyst system (publication II)

Inspired by the good results obtained with the ligand-activated $Fe(NO_3)_3$/TEMPO catalyst discussed above, ligand effects were studied with other first-row transition metal-based aerobic alcohol oxidation catalysts. The study was initiated by oxidizing 1-octanol (**1a**) to octanal (**2a**) with catalysts consisting of various first-row transition metal nitrate salts and TEMPO under the conditions that were optimized for **1a** oxidation with the $Fe(NO_3)_3$/bipy/TEMPO catalyst earlier: open air, room temperature and glacial AcOH as solvent. Among the tested metal nitrate/TEMPO combinations, the best results were achieved using Mn, Mn+Co and Mn+Cu nitrates, resulting in 18-26% substrate conversions and aldehyde yields (Table 4.3.1, Entries 1-3). In order to achieve higher conversions and yields, the above **1a** oxidations were re-conducted in the presence of various organic ligands. Among the numerous metal salt/ligand combinations tested, $Mn(NO_3)_2$ with 2-picolinic acid (PyCOOH) was found to give the best results. With this combination, **1a** was oxidized to **2a** in a near quantitative >99% conversion and 97% **2a** yield within 3h (entry 4). Furthermore, the loading of TEMPO could be reduced from the initial 10 mol% to 5 mol% without affecting the reaction outcome. The use of PyCOOH with the bimetallic Mn+Co and Mn+Cu catalysts did not result in such a significant improvement in catalytic activity (entries 5 and 6). Other ligand/metal combinations also failed to match the performance achieved with $Mn(NO_3)_2$/PyCOOH/TEMPO.

Table 4.3.1. *Aerobic oxidation of 1-octanol with selected TEMPO/metal nitrate catalysts.*



Entry	Metal salt	Ligand	TEMPO [mol%]	Conversion [%][a]	Yield [%][a]
1	$Mn(NO_3)_2$	-	10	26	26
2	$Mn/Co(NO_3)_2$	-	10	18	18
3	$Mn/Cu(NO_3)_2$	-	10	21	21
4	$Mn(NO_3)_2$		5	>99	97
5	$Mn/Co(NO_3)_2$		5	16	16
6	$Mn/Cu(NO_3)_2$		5	56	56

[a] Conversions and yields determined with GC-FID using acetophenone as internal standard.

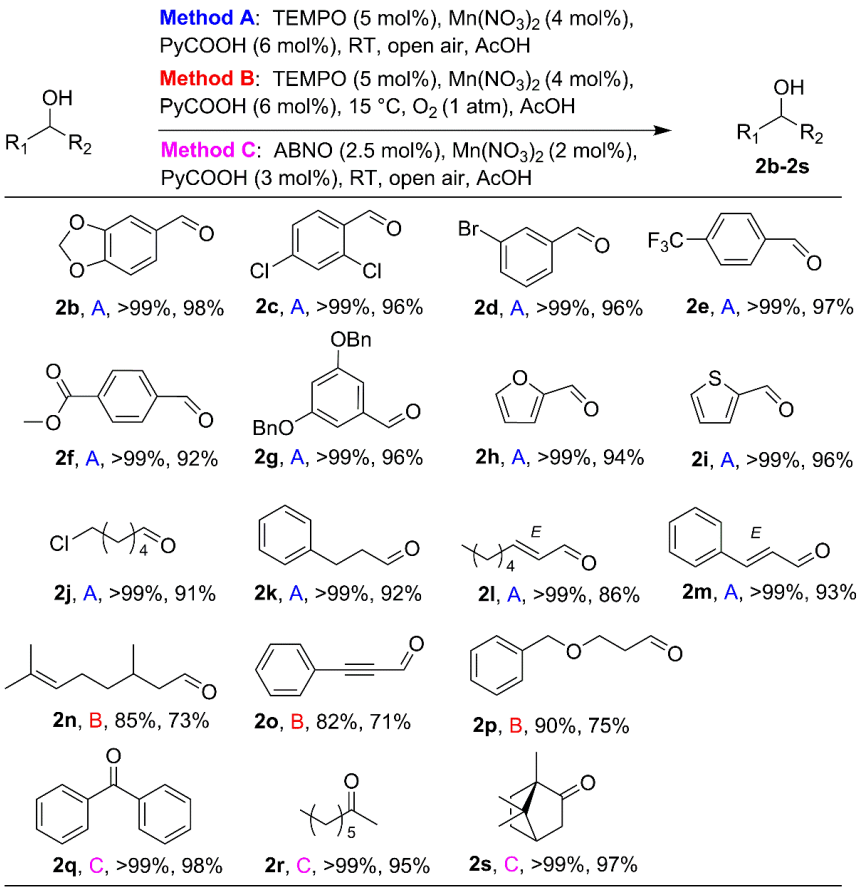
During the preparation of publication **I**, it had been discovered that primary aliphatic alcohols could be oxidized selectively either to aldehydes or carboxylic acids with an $Fe(NO_3)_3$/bipy/TEMPO catalyst. Thus, it was expected that the oxidation of **1a** with the newly discovered $Mn(NO_3)_2$/PyCOOH/TEMPO catalyst would also lead to stepwise oxidation to aldehyde **2a** and further to octanoic acid (**3a**) if the reaction time was prolonged sufficiently. However, significant formation of **3a** was not detected with the $Mn(NO_3)_2$/PyCOOH/TEMPO catalyst system even when the oxidation of **1a** was continued for 28 h. Instead, the concentration of aldehyde **2a** remained stable during the whole observation period and formation of side products was negligible. The high selectivity for aldehyde formation enabled isolation of pure **2a** from the reaction by simply extracting with EtOAc/H_2O followed by evaporation of the organic phase.

Substrate scope studies performed with the $Mn(NO_3)_2$/PyCOOH/TEMPO catalyst system showed that the catalyst is compatible a variety of functional groups, including double and triple bonds, halogens, esters, ethers and heteroaromatic structures. Significant difference in reactivity was not detected between benzylic (Table 4.3.2, **1b-1g**), heteroaromatic (**1h-1i**), aliphatic (**1j-1k**) or allylic (**1l-1m**) alcohols. These substrates were readily converted to the corresponding aldehydes (**2b-2m**) under ambient conditions within 3 h. Over 99% conversions were achieved with all the above substrates and formation of side products was negligible. This enabled simple and efficient recovery of the pure aldehyde products from the reaction mixture by extraction with EtOAc/H_2O followed by evaporation of the organic phase.

Minor selectivity issues arose during the oxidation of citronellol (Table 4.3.2, **1n**), 3-phenylprop-2-yn-1-ol (**1o**) and 3-(benzyloxy) propan-1-ol (**1p**) at room temperature. Full conversions were also achieved with these substrates, but low aldehyde yields (<45 %) were obtained due to hampered reaction selectivity. The selectivity issues were resolved by lowering the reaction temperature from room temperature down to 15°C and by using pure oxygen (balloon) as the oxidant. By conducting reactions under these conditions, aldehydes **2n-2p** could be obtained in over 70% isolated yields.

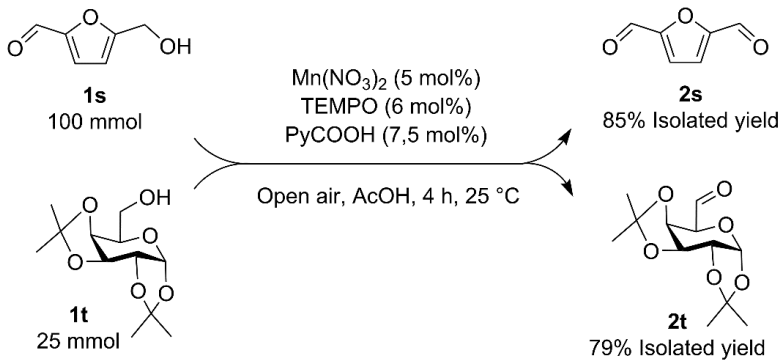
The initial attempts to oxidize secondary alcohols (Table 4.3.2, **1q-1s**) with the $Mn(NO_3)_2$/PyCOOH/TEMPO catalyst failed to produce the respective ketones **2q-2s** in high yields due to low alcohol conversion. To overcome the limitation related to secondary alcohol oxidation, catalytic TEMPO was replaced with sterically less hindered ABNO. This modification resulted in significantly improved reactivity: secondary alcohols and ketones **2q-2s** could now be isolated in over 95% yields using a simple extraction with EtOAc/H_2O followed by evaporation of the organic phase.

Table 4.3.2. *The aerobic oxidation of various alcohols with the $Mn(NO_3)_2$/PyCOOH/TEMPO catalyst system.*



Product number, synthetic method, conversion, isolated yield.

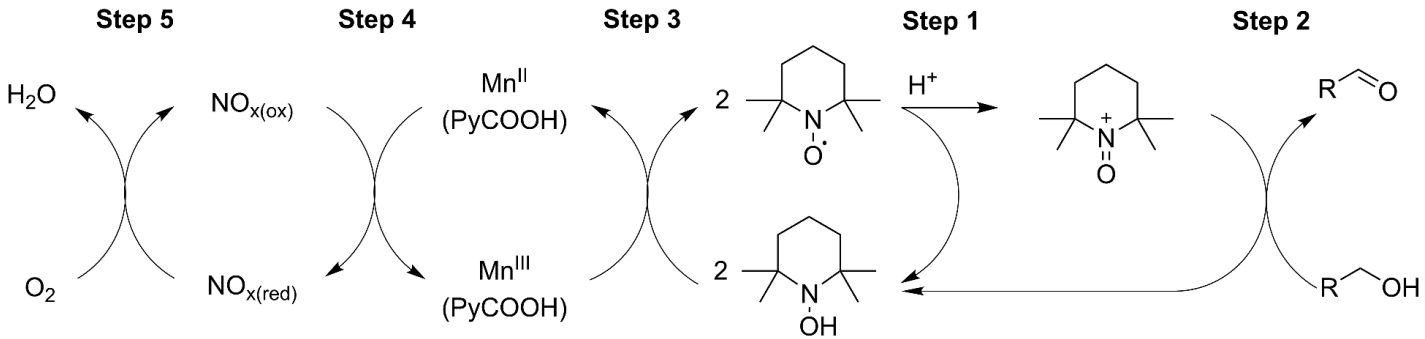
The above presented substrate scope studies were performed using only 2 mmol of substrate. To examine the suitability of these oxidation methods for preparative scale synthesis of carbonyl compounds, oxidations of bio-based 5-(hydroxymethyl)furfural (**1y**) and 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (**1z**) were conducted using 12.6 g (100 mmol) and 6.5 g (25 mmol) substrate amounts, respectively (Scheme 4.3.1). In both reactions, full substrate conversion was reached and aldehydes **2y** and **2z** were isolated in 85% and 79% yields, correspondingly. These results highlight the suitability of the method for preparation of carbonyl compounds from the respective alcohols in useful quantities.



Scheme 4.3.1. Multi gram scale oxidations of 5-(hydroxymethyl)furfural 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose.

To unravel the mechanistic aspects of $Mn(NO_3)_2$/PyCOOH/TEMPO-catalyzed aerobic oxidation of alcohols, a series of benzyl alcohol oxidations was performed under various conditions and the redox behavior of Mn was studied using UV-vis. Based on the results obtained from these experiments the following mechanism was suggested. Firstly, the catalytic alcohol oxidation is initiated by acid-induced disproportionation of TEMPO to the respective hydroxylamine (TEMPOH) and oxoammonium cation ($TEMPO^+$) (Scheme 4.3.2, **Step 1**).[40,149] This is followed by oxidation of the alcohol by $TEMPO^+$, and reduction of the latter to TEMPOH (**Step 2**).[36,94] TEMPOH is then oxidized back to TEMPO by Mn(III) (**Step 3**), which is formed from Mn(II) through reaction with a nitrate-derived oxidizing NO_x species (**Step 4**).[157,158] Coordination of PyCOOH ligand to Mn favors the formation of Mn(III) and therefore greatly accelerates the catalytic cycle.[159,160] Finally, O_2 regenerates the oxidizing NO_x and water is formed as a side product (**step 5**).[161]

In conclusion, the results in publication **II** show that the $Mn(NO_3)_2$/PyCOOH/TEMPO catalyst system enables selective and efficient aerobic oxidation of primary alcohols to carbonyl compounds under ambient air or 1 atm of O_2. Alcohol oxidations reach completion within just few hours and pure products are generally isolable by simple extraction with an organic solvent and water. The system is also applicable to the oxidation of secondary alcohols to ketones by replacing TEMPO with sterically less hindered ABNO. Therefore, the developed catalyst system offers a straightforward and practical method for preparative scale synthesis of aldehydes and ketones from alcohols. Mechanistic studies support the oxoammonium ion-mediated alcohol oxidation, wherein Mn(PyCOOH)/NO_x regenerates the active oxidant.



Scheme 4.3.2. Mechanistic proposal for the $Mn(NO_3)_2$/PyCOOH/TEMPO-catalyzed aerobic oxidation of alcohols.

4.4 $NaNO_3$ activated manganese/nitroxide catalyst system (publication III)

Despite offering a highly practical route for the selective aerobic oxidation of alcohols to aldehydes and ketones, the $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst system, which was introduced in the previous chapter, exhibits the following key limitations: catalytic activity is low and therefore high catalyst amounts have to be used to achieve complete substrate conversion (4-7.5 mol% of $Mn(NO_3)_2$,TEMPO and PyCOOH); catalyst stability has not been studied and recycling protocol has not been developed for the catalyst. To overcome these limitations, the $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst system was investigated in more detail, with an emphasis on catalyst loading optimization and recyclability.

The work was initiated by studying the oxidation of bio-based 5-(hydroxymethyl)furfural (**1a**, HMF) to 2,5-diformylfuran (**2a**, DFF). First, the aerobic oxidation of HMF was conducted using four different amounts of $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst (1, 2, 3 and 10 mol%) to see how the catalyst amount affects alcohol oxidation rate (Figure 4.4.1). The course of these reactions was followed by taking samples for GC analysis over time. With the smallest catalyst loading of 1 mol%, HMF oxidation started rapidly, producing DFF in 8% yield during the first 5 min. After this though, the reaction rate decreased sharply and only 15% DFF yield was recorded at the end of the 180 min observation period. The experiment conducted with 2 mol% of catalyst resulted in faster HMF oxidation at the beginning of the reaction and slower catalyst deactivation at later stages of the reaction, resulting in 46% DFF yield after 180 min. Further improvement in reactivity was achieved when the catalyst loading was increased to 3 mol%, which resulted in complete HMF conversion and 95% DFF yield after 40 min. With the largest catalyst loading of 10 mol%, the reaction was even faster. Full substrate conversion and 95% DFF yield were recorded after just 20 min.

During the oxidation of HMF with the highest (10 mol%) catalyst loading, orange gas was detected in the headspace of the reaction. This indicated the presence of NO_2 that might have formed from NO_3^- ions under the acidic reaction conditions, according to equation (4.4.1.).[158] In order to identify the orange gas, it was trapped into aqueous 0.1 M KOH solution, where NO_2 would disproportionate to NO_3^- and NO_2^- ions, according to equation (4.4.2).[162,163] The presence of NO_3^- and NO_2^- in the aqueous solution was then investigated by conducting permanganate and diphenylamine tests.[164,165] Both tests gave positive results, indicating that NO_3^- and NO_2^- were present in the aqueous solution, thus confirming that the orange gas was indeed NO_2. Based on this finding, it seemed plausible that the acid-induced conversion of NO_3^- to NO_2 and subsequent evaporation of the latter contribute significantly to

deactivation of the catalyst that was observed during the HMF oxidations with the low 1 and 2 mol% catalyst loadings above.

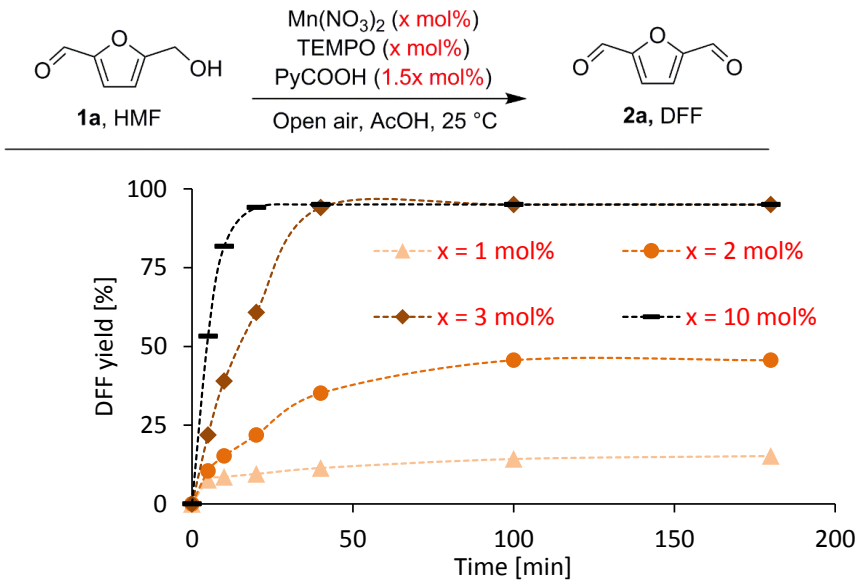


Figure 4.4.1. Aerobic oxidation of HMF to DFF with the $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst. Yields determined using GC-FID with acetophenone as internal standard.

$$4\ HNO_3 \rightleftharpoons 4\ NO_2 + 2\ H_2O + O_2 \qquad (4.4.1)$$

$$2\ NO_2 + H_2O \rightleftharpoons HNO_3 + HNO_2 \qquad (4.4.2)$$

The effect of added NO_3^- on the catalytic activity was investigated by re-conducting the above HMF oxidations with 1, 2, 3 and 10 mol% catalyst in the presence of 2 mol% $NaNO_3$ (Figure 4.4.2). The presence of additional $NaNO_3$ had a clear positive impact on the catalyst activity. The significance of added $NaNO_3$ was especially prominent in the reactions performed using 1 mol% and 2 mol% catalyst loadings, as the catalyst lifetime was now significantly increased from the initial experiments performed without $NaNO_3$. At the end of the reactions performed with 1 and 2 mol% catalyst loadings, DFF yields of 65% and 95% were recorded, respectively, while using the same catalyst loadings had resulted in only 15% and 46% DFF yields when $NaNO_3$ had not been added. With the larger catalyst loadings of 3 and 10 mol%, $NaNO_3$ addition had a less profound effect on reactivity as adequate NO_3^- concentration was already achieved in the initial experiments conducted without added $NaNO_3$.

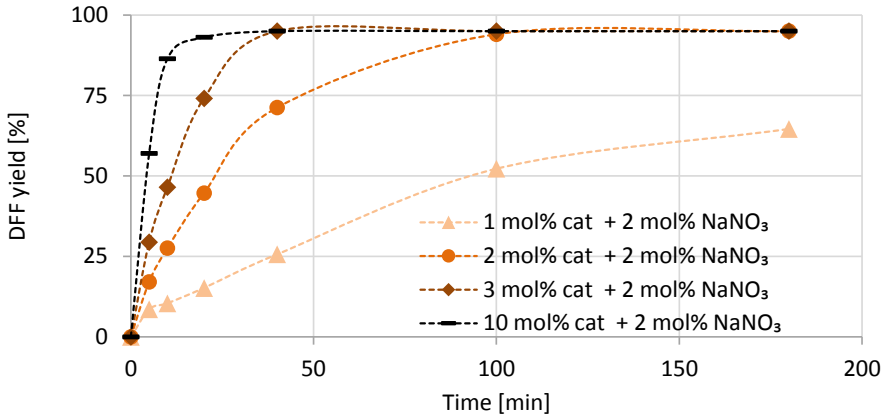


Figure 4.4.2. Aerobic oxidation of HMF to DFF with nitrate-activated $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst. Yields determined using GC-FID with acetophenone as internal standard.

After discovering the stabilizing effect that the presence of $NaNO_3$ has on the $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst, other nitrate and nitrite additives were investigated for the same purpose. As the results in Table 4.4.3 illustrate, the presence of both nitrates and nitrites has a beneficial effect on catalyst activity regardless of the counter cation, nitrates being superior to nitrites.

The effect of the added nitrate amount on catalyst activity was studied by conducting a series of HMF oxidations with 1 mol% loading of $Mn(NO_3)_2$/TEMPO/PyCOOH and varied loadings of HNO_3 or $NaNO_3$ (0-15%) (Figure 4.4.4). When the amount of $NaNO_3$ was increased from 0 mol% to ≥4 mol% DFF yields rose steadily from 15% to 95%. Similar catalyst activation was observed when small amounts (1-4 mol%) of HNO_3 were added to the reaction, but the reactivity decreased with higher loadings (≥6 mol%) of HNO_3. This shows that catalyst activity is hampered under excessively acidic conditions, plausibly due to accelerated disproportionation of HNO_3 to volatile NO_2 and evaporation of the latter, according to equation (4.4.1). Excessive acidity might also alter the coordination chemistry of the catalytically active Mn-center, causing decreased reactivity. Thus, neutral $NaNO_3$ was chosen for further studies instead of HNO_3.

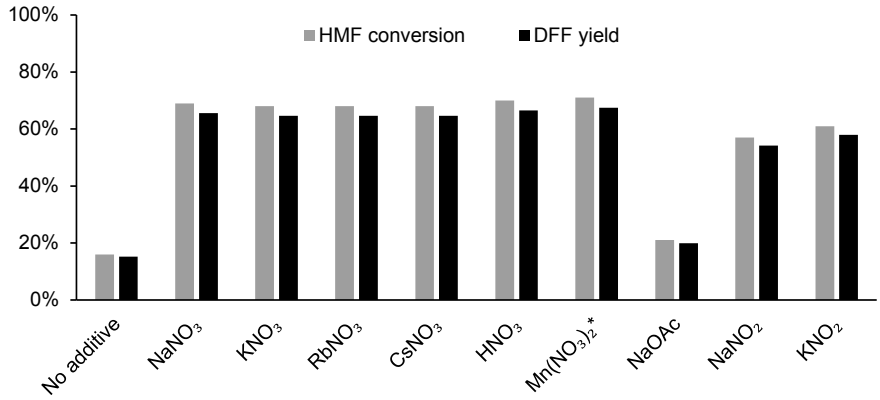


Figure 4.4.3. The effect of metal nitrates and nitrites (2 mol%) on catalytic oxidation of HMF with the $Mn(NO_3)_2$/TEMPO/PyCOOH (1/1/1.5 mol%) catalyst under ambient conditions. Yields and conversions determined using GC-FID with acetophenone as internal standard. * 1 mol% of $Mn(NO_3)_2$ added.

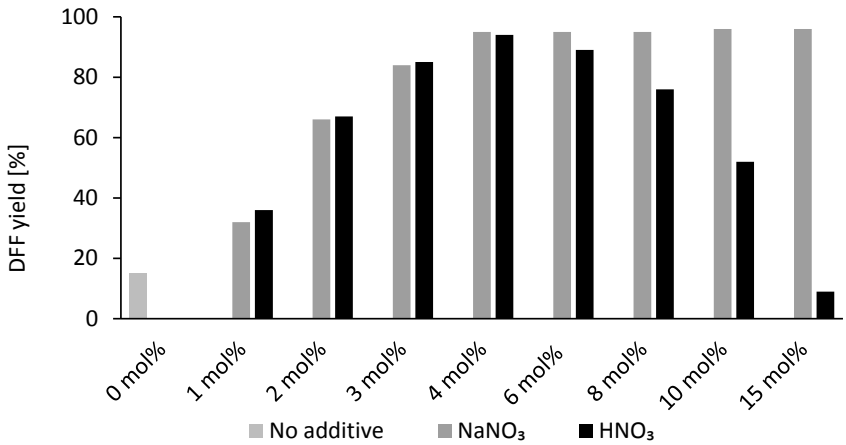
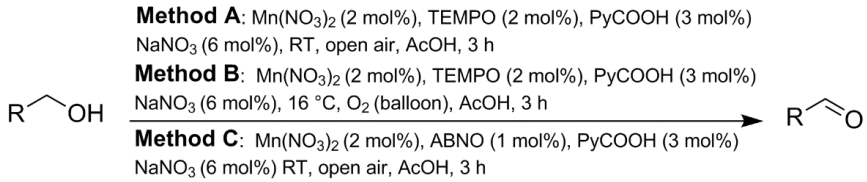


Figure 4.4.4. The effect of $NaNO_3$ and HNO_3 amount on the aerobic oxidation of HMF to DFF with the $Mn(NO_3)_2$/TEMPO/PyCOOH (1/1/1.5 mol%) catalyst system under ambient conditions. Yields determined using GC-FID with acetophenone as internal standard.

To discover how addition of $NaNO_3$ affects catalyst activity in the oxidation of alcohols other than HMF, a substrate scope study was performed. For this purpose, various alcohols were oxidized using the $Mn(NO_3)_2$/TEMPO/PyCOOH (2/2/3 mol%) catalyst both in the presence and in the absence of $NaNO_3$ (6 mol%) (Table 4.4.1). In all cases, substrate conversion and product yield were significantly higher in the presence of $NaNO_3$ than in the absence of it. On average, addition of $NaNO_3$ increased alcohol conversion by 59% and product yield by 60%.

Table 4.4.1. *Aerobic oxidation of different alcohols with nitrate-activated $Mn(NO_3)_2$/TEMPO/ PyCOOH catalyst system.*[a]



Alcohol	Product	Method	With $NaNO_3$ Conv. %[a]	With $NaNO_3$ Isol. Yield %	Without $NaNO_3$ Conv. %[a]	Without $NaNO_3$ Isol. Yield %
1b	**2b**	A	>99	94	22	14
1c	**2c**	A	>99	98	31	25
1d	**2d**	A	>99	98	69	63
1e	**2e**	A[b]	>99	92	36	30
1f	**2f**	A[b]	95	86	34	27
1g	**2g**	A	>99	93	14	8
1h	**2h**	A	>99	94	71	65
1i	**2i**	B	83	75	23	16
1j	**2j**	B	83	76	32	23
1k	**2k**	B[b]	79	71	12	5
1l	**2l**	C	>99	98	75	69
1m	**2m**	C	>99	94	32	26
1n	**2n**	C	>99	96	35	28

[a] Conversion determined using GC-FID with acetophenone as internal standard. [b] 12 mol% $NaNO_3$.

Recyclability of the $NaNO_3$-activated $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst was investigated by using oxidation of benzyl alcohol (**1o**) as a model

reaction. It was found that the catalyst can be recycled by the following protocol. After completion of the alcohol oxidation, a small amount of 1 M HCl and diethyl ether are added to dissolve the hydrophilic catalyst into the aqueous phase and the lipophilic benzaldehyde (**2o**) into the organic phase. The catalyst is then recovered by evaporating the aqueous phase *in vacuo*. Further alcohol oxidation can then be started by dissolving a catalytic amount of fresh $NaNO_3$, the recovered solid catalyst and a new batch of the desired alcohol into glacial AcOH. This recycling protocol was successfully used to perform five consecutive **1o** oxidations. After the last use, 80% substrate conversion was still achieved, showing that the catalyst is recyclable with only a slight decrease in activity (Figure 4.4.5a). On the contrary, catalyst activity deteriorated if fresh $NaNO_3$ was not added into the reaction between subsequent uses of the catalyst, resulting in negligible benzaldehyde yields of ≤4% on runs 2-5. (Figure 4.4.5b).

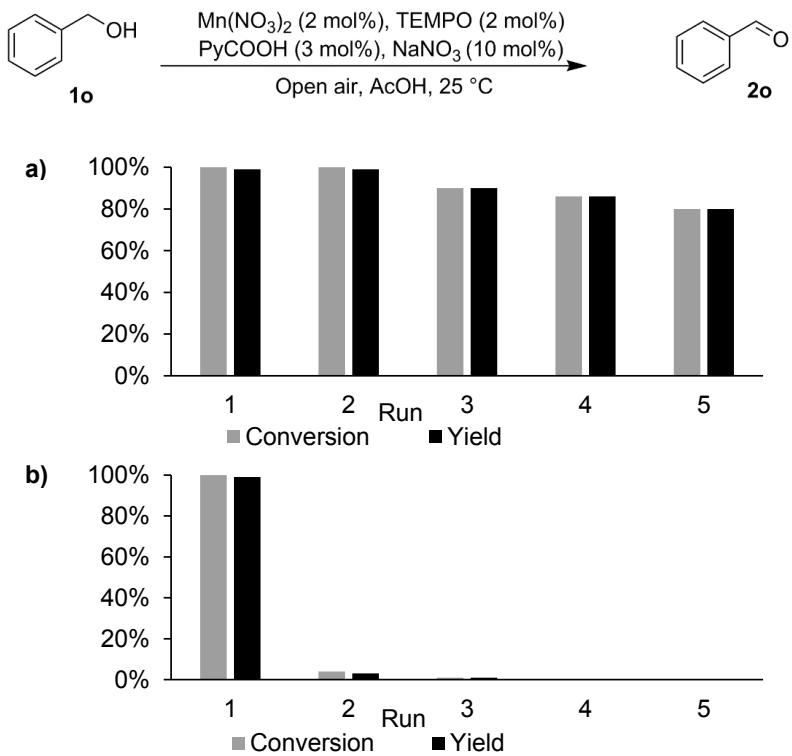


Figure 4.4.5. Oxidation of benzyl alcohol with recycled catalyst. a) 10 Mol% $NaNO_3$ added before runs 2-5; b) without addition of fresh $NaNO_3$ prior to runs 2-5. Yields determined using GC-FID with acetophenone as internal standard.

To conclude: the study shows that formation and subsequent evaporation of NO_2 is the leading cause of deactivation for the *in situ* prepared $Mn(NO_3)_2$/TEMPO/PyCOOH aerobic alcohol oxidation catalyst under open air conditions. Deactivation of the catalyst is easily overcome by adding a catalytic amount of a cheap and readily available nitrate source, for example $NaNO_3$, into the reaction. This stabilizes the catalyst and enables the use of low $Mn(NO_3)_2$/TEMPO/PyCOOH loadings without compromising the catalyst performance. Highly selective and near quantitative oxidation of primary alcohols to the respective aldehydes is generally achieved with the $NaNO_3$-enhanced $Mn(NO_3)_2$/TEMPO/PyCOOH catalyst within a few hours under ambient air. The system is also suitable for oxidation of secondary alcohols when catalytic TEMPO is replaced with the sterically less hindered nitroxyl radical ABNO. At the end of the alcohol oxidation, pure carbonyl products and reusable catalyst can be recovered simply by extracting with organic solvent and dilute acid, followed by evaporation of both phases.

5 Conclusions

Over 30 years has passed since Semmalhack and co-workers[23] published their landmark article describing the selective aerobic oxidation of primary alcohols to aldehydes using a homogenous Cu/nitroxide catalyst system. Since then, the topic of homogenous nitroxide catalysis has gained a significant amount of research scrutiny and numerous protocols utilizing different co-catalyst systems have been published. Among these methods, Cu/nitroxide and NO_x/nitroxide-based transition-metal-free catalyst systems have received the most attention. The thorough studies conducted on these catalyst systems have built valuable understanding on the catalysts' structure-reactivity relationships and substrate scopes. Both Cu/nitroxide and NO_x/nitroxide catalysts have been proven as highly versatile catalysts that can be used to synthesize various aldehydes and ketones under benign conditions. Yet, no success has been achieved with these catalyst systems in converting primary alcohols to the respective carboxylic acids, which limits the application scope of these catalyst systems for the synthesis of aldehydes and ketones.

A number of studies have also been published on the use of nitroxides with Fe-based co-catalyst systems. Most of the publications describing the use of these catalyst systems have focused on the oxidation of simple primary and secondary alcohols to the respective aldehydes and ketones, while oxidation of more complex alcohols with different functional groups has been less explored. Therefore, the scope and limitations of the Fe/nitroxide-catalysts are not as well understood as with the above-discussed Cu/nitroxide and NO_x/nitroxide catalyst systems. Also studies on the relationships between catalysts' structures and reactivities have remained scarce with Fe/nitroxide system. For example, organic ligands had not been employed to activate Fe/nitroxide catalysts prior to publication of article **I,** in which we showed that a significant increase in the catalytic activity can be achieved by incorporating a suitable organic ligand into an Fe/nitroxide catalyst system. This finding and subsequent optimization work led to development of novel *in situ* $Fe(NO_3)_3$/bipy/TEMPO and $Fe(NO_3)_3$/bipy/ABNO catalyst systems for the oxidation of primary and secondary alcohols, respectively. Prior to publication of **I**, the direct oxidation of primary alcohols to carboxylic acids had not been reported with nitroxide-based catalyst systems. In this respect, it was intriguing to discover that the $Fe(NO_3)_3$/bipy/TEMPO catalyst system enables the selective oxidation of primary alcohols selectively to either aldehydes or carboxylic acids. Even after the publication of this catalyst system, only very few other nitroxide-based catalyst systems have been published for the aerobic oxidation of primary alcohols to carboxylic acids, which highlights the novelty of the work.

Homogeous nitroxide catalysts that employ other transition metal co-catalyst systems than those based on Cu or Fe have received little research

interest up to date. For example, Mn-based catalyst systems had not been widely investigated prior to our work on the topic. In publication **II**, we reported that an efficient alcohol oxidation catalyst is formed when $Mn(NO_3)_2$, PyCOOH and TEMPO are dissolved into glacial AcOH. This *in situ* catalyst is easy to prepare and straightforward to use; only stirring of the catalyst components and the desired primary alcohol in an open beaker at ambient temperature is required for achieving very high aldehyde yields within just few hours. The catalyst is compatible with various substrates, inluding aliphatic, allylic, benzylic and heteroaromatic alcohols bearing different functional groups. Secondary alcohols can be oxidized to ketones if TEMPO is replaced with sterically less hindered ABNO. After completion of the alcohol oxidation, the aldehyde and ketone products can be isolated by simply extracting with organic solvent and water, followed by evaporation of the organic phase. Therefore, the $Mn(NO_3)_2$/PyCOOH/TEMPO and $Mn(NO_3)_2$/PyCOOH/ABNO catalysts offer highly practical routes for laboratory scale synthesis of aldehydes and ketones from the respective alcohols.

In publication **III**, the above $Mn(NO_3)_2$/PyCOOH/TEMPO and $Mn(NO_3)_2$/PyCOOH/ABNO catalyst systems were investigated and developed further. As a result, a mechanism for catalyst deactivation was discovered and an efficient method for preventing it by adding a catalytic amount of cheap and readily available $NaNO_3$ into reaction was established. This enabled lowering the amount of catalytic $Mn(NO_3)_2$, PyCOOH and TEMPO or ABNO from 2.5-7.5 mol% down to 1-3 mol% without compromising the catalyst performance or practicality of the protocol. Moreover, a simple recycling protocol was developed for the above Mn/nitroxide catalysts.

The concluding remarks about the developed catalyst systems and their applicability to oxidation of different substrates are presented in Table 5.1. As shown, oxidations based on the use of TEMPO as a nitroxyl radical are well suited for the oxidation of primary alcohols to aldehydes. The best performance is achieved by using the $NaNO_3$ activated $Mn(NO_3)_2$/PyCOOH/TEMPO catalyst system as it enables the oxidation of primary alcohols to aldehydes in a straightforward and highly practical manner with low catalyst loading. If direct oxidation of primary alcohols to carboxylic acids is sought, the $Fe(NO_3)_3$/bipy/TEMPO catalyst should be employed, as it is the only catalyst system presented in this work that enables the transformation. Oxidation of secondary alcohols to ketones can be conducted using any of the three ABNO-based catalyst systems, while the best combination of simplicity and efficiency is achieved with $NaNO_3$ activated $Mn(NO_3)_2$/PyCOOH/ABNO catalyst.

Table 5.1. *Comparison of different catalyst systems for the aerobic oxidation of alcohols.*

Reported in article	Catalyst system	Oxidation of prim. alcohols to aldehydes	Oxidation of prim. alcohols to carbox. acids	Oxidation of sec. alcohols to ketones
I	$Fe(NO_3)_3$/bipy/TEMPO	++	+++	-
I	$Fe(NO_3)_3$/bipy/ABNO	+	-	++
II	$Mn(NO_3)_2$/PyCOOH/TEMPO	++	-	-
II	$Mn(NO_3)_2$/PyCOOH/ABNO	*	-	++
III	$NaNO_3$/$Mn(NO_3)_2$/PyCOOH/TEMPO	+++	-	-
III	$NaNO_3$/$Mn(NO_3)_2$/PyCOOH/ABNO	*	-	+++

* Not investigated in this work.

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